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Review of the National Ambient Air Quality Standards for Nitrogen Oxides: Assessment of Scientific and Technical Information

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OAQPS Staff Paper

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REVIEW OF THE NATIONAL AMBIENT AIR QUALITY STANDARDS FOR NITROGEN OXIDES: ASSESSMENT OF SCIENTIFIC AND TECHNICAL INFORMATION

OAQPS STAFF PAPER

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16. ABSTRACT

This paper evaluates and interprets the available scientific and technical information that the EPA staff believes is most relevant to the review of primary (health) and secondary (welfare) National Ambient Air Quality Standards for Nitrogen Oxides (NO_2) and presents staff recommendations on alternative approaches to revising the standards. The assessment is intended to bridge the gap between the scientific review in the EPA criteria document for nitrogen oxides and the judgements required of the Administrator in setting ambient air quality standards for nitrogen oxides.

The major recommendations of the staff paper include the following:

1) that an annual standard be retained at some level between 0.05 ppm and 0.08 ppm to provide a reasonable level of protection against potential short term peaks in the range of 0.15 to 0.30 ppm;

2) alternatively, that a new multiple exceedance 1 hour average NO_2 standard at some level below 0.5 ppm be established;

3) that there is no evidence to suggest the need for a separate secondary standard provided a primary standard is established within the ranges suggested above to protect human health.

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EXECUTIVE SUMMARY

This paper assesses the scientific evidence concerning the effects of nitrogen dioxide (NO_2) on human health and welfare, discusses the EPA staff interpretation of this evidence, and presents staff recommendations on alternative approaches to revising the standards. Review of the National Ambient Air Quality Standards (NAAQS) is a periodic process instituted to ensure the scientific adequacy of air quality standards and is required by section 109 of the 1977 Clean Air Act Amendments. The staff paper is an important element in this review process and provides an opportunity for public comment on proposed staff recommendations before they are submitted to the Administrator.

NO_2 is an air pollutant which is oxidized from nitric oxide (NO) emitted from both mobile and stationary sources. At elevated concentrations NO_2 can adversely affect human health, vegetation, materials, and visibility. Nitrogen oxide compounds (NO_x) also contribute to increased rates of acidic deposition. Typical long-term ambient concentrations of NO_2 range from 0.001 ppm in isolated rural areas to a maximum annual concentration of approximately 0.08 ppm in one of the nation's most populated urban areas. Short-term hourly peak concentrations rarely exceed 0.5 ppm.

While adverse effects have been reported at NO_2 levels above 1.0 ppm, little credible evidence exists which links specific human health effects to NO_2 concentrations at or near ambient levels. Evidence at these lower concentrations is not conclusive and in most cases is confounded by uncertainties regarding the cause of the effect and the effect concentration level. The existing annual standard (0.053 ppm) was based largely on a community epidemiology study (Shy et al., 1970) suggesting respiratory effects in children exposed to long-term low level NO_2 concentrations. Reevaluation of this study based on new information (especially regarding the accuracy of ambient air monitoring for NO_2 used in the study) appears to invalidate the reported findings. Therefore, this study no longer is seen as an adequate basis for retaining the existing standard. Other outdoor community epidemiology studies attempting to document effects from long-term low level exposure to NO_2 are either flawed or report no effects associated with NO_2 exposure.

There presently is no reliable scientific evidence reporting adverse effects in humans due to chronic (long-term) NO_2 exposure at ambient air levels. However, there is convincing evidence from animal studies which reveals serious biological effects from elevated (higher than ambient) long-term NO_2 exposures. These findings suggest a definite risk to human health from chronic exposure to NO_2, but such risks have not been quantified at ambient air levels.

Effects from both single and repeated short-term peak exposures have been documented in the scientific literature. Modeling results from animal infectivity studies suggest that short-term peak exposures probably are more important in causing adverse effects than long-term low level exposures of equivalent doses. Effects of definite health concern in humans resulting from single short-term peak exposures have been observed only at relatively high NO_2 concentrations (above 1 ppm). More subtle effects that are of questionable health significance, such as mild symptomatic effects, have been reported for some sensitive human population groups (e.g. asthmatics) after a single 2-hour exposure to 0.5 ppm. Animal studies report a variety of responses from single short-term peak exposures in the range of 0.2 ppm to 5 ppm; but the health significance of these latter findings for humans is uncertain.

Repeated peak exposures are of special concern because concentrations at which some effects have been reported are observed in the ambient air. However, the evidence of adverse health impact at these levels is limited and inconclusive. The principal evidence from which inferences might be drawn regarding effects from repeated short-term peak exposures is from a series of ongoing epidemiological studies. The published results from these studies report increased rates of acute respiratory illness and impaired pulmonary function for children living in homes with gas stoves as compared to children living in homes with electric stoves. The findings from animal studies demonstrating reduced resistance to infection due to NO_2 exposure support the hypothesis that NO_2 is the primary agent responsible for the effects observed in the "gas stove" studies. These findings suggest that multiple exposures to short-term NO_2 levels below 0.5 ppm should be avoided. While a precise level cannot be identified, preliminary epidemiological findings and related indoor air pollution monitoring studies assessing variations of NO_2 levels in gas stove homes suggest that repeated peaks in the range of 0.15 to 0.30 ppm may be of concern for children.

Given the uncertainties existing in the available scientific data, no rigorous rationale can be offered to support a specific NO_2 standard. However, not to establish a standard, we believe, would ignore the cumulative evidence from animal, controlled human exposure, and community indoor air pollution studies which suggest that NO_2 may cause adverse health effects in sensitive population groups exposed to NO_2 at or near existing ambient levels.

Two approaches to minimizing potential health effects associated with NO_2 exposure in the ambient air are suggested. The first is to retain an annual standard at some level between 0.05 ppm and 0.08 ppm to provide a reasonable level of protection against potential short-term peaks. A 0.08 ppm standard would be expected to limit the number of days with hourly peak concentrations above 0.30 ppm to about ten per year based on analysis of existing ambient air quality data. In most areas of the country attainment of an annual standard of 0.05 ppm should virtually preclude the occurrence of 0.30 ppm peaks and limit the number of days with hourly peak concentrations of 0.15 ppm to a range of approximately 10-20 (some southern California sites may exceed 0.15 ppm on as many as 40 days). An annual standard in this range also would provide reasonable assurance that 1-hour peak concentrations of NO_2 would not exceed 0.5 ppm. An alternative approach is to establish a new multiple exceedance 1-hour average NO_2 standard at some level below 0.5 ppm. Such a standard acknowledges medical evidence suggesting the importance of repeated peak exposures and would incorporate an allowable rate of exceedance which would be a function of the standard level.

Either of the above approaches can provide a reasonable degree of protection against repeated peak exposures in the range of 0.15 to 0.30 ppm. A long-term standard offers the practical advantage of not requiring formulation and implementation of a new regulatory program. Establishing a new short-term standard would require more significant changes in modeling and monitoring procedures than retention of an annual standard.

NO_x effects on man's environment, personal comfort, and well-being include impacts on vegetation, materials, visibility, rates of acidic deposition, and symptomatic effects in humans. Because acidic deposition is an important and complex problem associated with multi-pollutant interactions, it is being addressed as a separate program by EPA and not as a specific element of the NO_2 standard review. With respect to the need for a standard to protect against other possible adverse welfare effects, there is no evidence to suggest the need for a separate secondary standard provided a primary standard is established within the ranges suggested above to protect human health.

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PRELIMINARY ASSESSMENT OF HEALTH AND WELFARE EFFECTS ASSOCIATED WITH NITROGEN OXIDES FOR STANDARD-SETTING PURPOSES
DRAFT STAFF PAPER

I. PURPOSE

The purpose of this paper is to evaluate the key studies and scientific information contained in the draft EPA document "Air Quality Criteria for Oxides of Nitrogen"[1] and to identify the critical elements that EPA staff believe should be considered in the review and possible revision of the current long-term (annual average) primary and secondary National Ambient Air Quality Standards (NAAQS) for nitrogen dioxide (NO_2). The paper also identifies the critical factors that must be considered in deciding whether short-term (1-3 hours) NO_2 standards are required to protect public health and welfare, based on the information in the criteria document.

II. BACKGROUND

Since 1970 the Clean Air Act as amended has provided authority and guidance for the listing of certain ambient air pollutants which may endanger public health or welfare and the setting and revising of NAAQS for those pollutants. Primary standards must be based on health effects criteria and provide an adequate margin of safety to ensure protection of public health. As several recent judicial decisions have made clear, the economic and technological feasibility of attaining primary standards are not to be considered in setting them, although such factors should be considered in the development of state plans to implement the standards.[2,2a] Further guidance provided in the legislative history[3] of the Act indicates that the standards should be set at "the maximum permissible ambient air level . . . which will protect the health of any (sensitive) group of the population." Also, margins of safety are to be provided such that the standards will afford "a reasonable degree of protection . . . against hazards which research has not yet identified."[3] In the final analysis, the EPA Administrator must make a policy decision in setting the primary standard based on her judgment regarding the implications of all the health effects evidence and the requirement that an adequate margin of safety be provided.

Secondary ambient air quality standards must be adequate to protect the public welfare from any known or anticipated adverse effects associated with the presence of a listed ambient air pollutant. Welfare effects, which are defined in section 302(h) of the Act, include effects on vegetation, visibility, water, crops, man-made materials, animals, economic values and personal comfort and well-being. In specifying a level or levels for secondary standards the Administrator must determine at which point the effects become "adverse" and base her judgment on the welfare effects criteria.

Both the current primary (to protect public health) and secondary (to protect public welfare) NAAQS for NO_2 are 0.053 ppm (100 $\mu g/m^3$), averaged over 1 year. In 1977, Congress amended section 109(c) of the Clean Air Act to require the Administrator to promulgate a short-term NO_2 primary standard for NO_2 concentrations over a period of not more than 3 hours unless she finds no significant evidence that such a standard is required to protect public health.

A preliminary version of this paper was reviewed by the Clean Air Scientific Advisory Committee (CASAC) on November 14, 1980,[4] February 6, 1981,[5] and November 18, 1981.[5a] This final product incorporates the suggestions and recommendations of the CASAC as well as other appropriate comments received in initial drafts. The CASAC closure memo on the Staff Paper (Friedlander, 1982) is reprinted in Appendix C.

III. APPROACH

The approach used in this paper is to identify the critical elements the staff believes should be considered in the review of the primary and secondary standards. Particular attention is drawn to those judgments that must be based on the careful interpretation of incomplete or uncertain evidence. In such instances, the paper states our evaluation of the evidence as it relates to a specific judgment, sets forth appropriate alternatives that should be considered, and recommends a course of action. To facilitate the review, the paper is organized into sections as outlined below.

Section IV provides an overview of the ambient levels of NO_2 currently being experienced in various portions of the U.S. This section is intended to set the stage for the remaining discussion by identifying the present air quality situation so the reader can relate the available health and welfare information to what is actually occurring in the real world.

Section V addresses the essential elements examined in reaching conclusions regarding the primary standards; these include the following:

- the most probable mechanism(s) of toxicity by which health effects occur,
- a description of the scientific evidence on health effects attributed to nitrogen oxides (NO_x) and whether a standard should be considered for NO_2 alone,
- an identification and evaluation of scientific uncertainties with regard to the health effects evidence and staff judgments concerning which effects are important for the Administrator to consider in reviewing and setting primary standards, and
- a description of the most sensitive population groups and estimates of the size of those groups.

Drawing from the discussions in Sections IV and V, Section VI identifies and assesses the factors that the staff believes should be considered in selecting averaging times and levels of primary standards. Staff conclusions and recommendations also are presented in Section VI.

In Section VII the effects of NO_x on personal comfort, vegetation, visibility, and man-made materials are examined. The elements addressed in this section include the following:

- the most probable mechanisms of interaction by which such effects occur,

- a description of the welfare effects attributed to NO_x,
- an evaluation of which effects are to be considered adverse and judgments on which adverse effects are critical for standard setting, and
- the levels of exposure and averaging times associated with critical adverse effect(s) of concern.

IV. Ambient NO2 Concentrations in Urbanized Areas

This section briefly characterizes ambient NO_2 levels so the reader may better evaluate the significance of health and welfare effects discussed later in the paper. A more complete discussion of ambient air quality is provided in Appendix B.

Based on monitoring data from 186 urbanized areas, annual average NO_2 concentrations increased by about 10 percent (on the average) between 1974 and 1978 and have held steady from 1979 through 1980. Over 95 percent of the 186 urbanized areas where monitoring currently is being conducted are in compliance with the current 0.053 ppm annual average standard, although annual average concentrations in a number of these areas are beginning to approach this level. In the remaining 5% of the areas (where the standard is exceeded), the annual average exceeds 0.060 ppm in three areas. The highest annual average observed during 1977-1979 was 0.081 ppm.

The mean annual concentration in the above urbanized areas during 1977-1979 was 0.029 ppm as compared to 0.01 ppm in inhabited non-metropolitan areas and 0.001 ppm in isolated areas essentially unaffected by man-made NO_x emissions. Thus, long-term concentrations are considerably higher in the nation's major cities than in rural areas and small cities.

During 1977-1979, peak 1-hour average concentrations of NO_2 ranged from 0.06 ppm to about 0.5 ppm in urbanized areas. In most of these areas, 1-hour average concentrations seldom exceeded 0.30 ppm. Where the current annual NO_2 standard is being met, 1-hour average concentrations exceed 0.15 on 10-20 days per year (exceptions to this latter observation occur in several California cities where 1-hour levels have exceeded 0.15 ppm on more than 40 days in a year even though the annual standard was met.) One-hour concentrations of NO_2 exceeded 0.10 ppm on many days during a given year in essentially all 186 urbanized areas.

V. CRITICAL ELEMENTS IN THE PRIMARY STANDARD(S) REVIEW

A. Introduction

A variety of nitrogen oxide (NO_x) compounds and their transformation products occur naturally and as a result of human activities. Nitric oxide (NO), nitrogen dioxide (NO_2), gaseous nitric acid (HNO_3), in addition to nitrite and nitrate aerosols, have all been found in the ambient air. The formation of nitrosamines in the atmosphere by reaction of nitrogen oxides with amines has been suggested, but not yet convincingly demonstrated.[6]

Despite considerable scientific research on the potential health effects of NO_x compounds, there exists little evidence linking specific health effects to near ambient concentrations of most of these substances. The one significant exception is NO_2. This section will, therefore, focus primarily on the health effects that have been reported to be associated with NO_2. Particular emphasis will be placed on the effects of NO_2 on the respiratory system, since these effects have been extensively characterized and appear to be of concern for both short- and long-term exposures.

B. Mechanisms of NO_2 Toxicity

The mechanisms of toxicity responsible for effects caused by short-term and long-term exposures to NO_2 are incompletely understood. The variety of effects, such as (1) increased airway resistance and alterations in lung hormone metabolism for short-term exposures and (2) increased susceptibility to infection and morphological damage for long-term or multiple exposures, may well be explained by related mechanisms of oxidative damage. However, the body of data is not yet definitive. Because NO_2 is relatively insoluble in water, some fraction normally penetrates to the distal airways during inhalation. In spite of the insoluble nature of NO_2, the reactivity of NO_2 is sufficient to permit chemical interaction and absorption along the entire tracheobronchial tree.

Although the nasopharyngeal cavity is normally the first region of removal during NO_2 inhalation for nasal breathers, few studies provide good estimates of the rate of uptake in this region. Those which have provided estimates report nasopharyngeal removal rates of 42% (dogs and rabbits) and 50% (rabbits).[7,8] The process of nasopharyngeal removal of NO_2 involves both peroxidation reactions with lipids and absorption in the mucous lining of the nasopharyngeal cavity, where NO_2 is chemically converted to nitrous acid (HNO_2) and nitric acid (HNO_3).

When NO_2 enters the lungs, most of the reacting NO_2 rapidly oxidizes cellular lipids, although some slowly hydrolyzes to form HNO_2 and HNO_3.[9] The most destructive reaction involves oxidation of unsaturated lipids of the cellular membrane and results in the formation of peroxidic products. The disruption of the cellular membrane, which is essential for maintaining cellular integrity and function, probably accounts for many of the biological effects (e.g., hyperplasia, morphological damage, pulmonary edema) which have been ascribed to NO_2.[10]

Understanding the temporal sequence of events following inhalation of NO_2 is important to elucidate the mechanisms of toxicity for health effects caused by both short- and long-term exposures. A temporal sequence of events is portrayed in Figure 1.[1] This is a composite based on data from different investigations using experimental rats to illustrate the process of injury and repair over time following short-term single exposures of 4 hours or less. It is likely that this sequence of events is similar in all mammals exposed under the same conditions to low concentrations of NO_2, but these experiments have not been performed for numerous species. The important observation from Figure 1 is that the effects of NO_2 exposure may not peak for several hours after initial exposure, and subjects may require up to several days in an unexposed environment to fully recover.

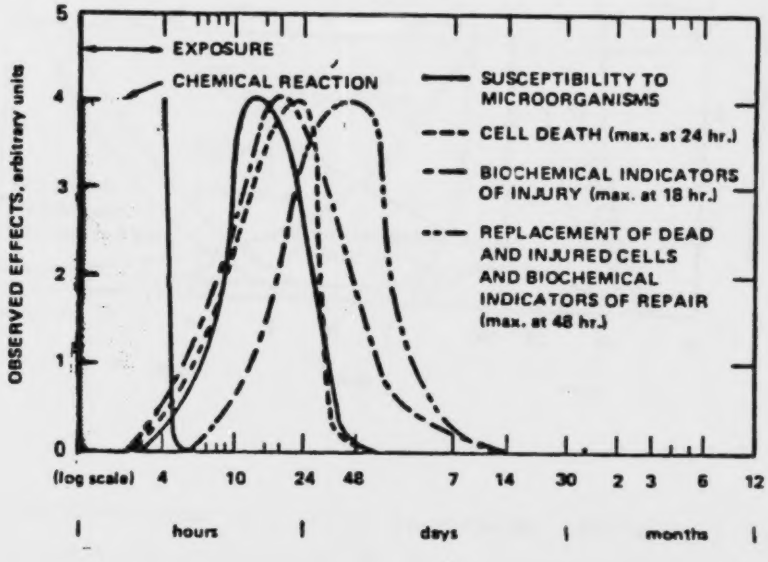


Figure 1. Temporal Sequence of Injury and Repair Hypothesized From Short-Term Single Exposures of Less than 4 Hours[1]

The initial temporal sequence of events during long-term continuous exposure to NO_2 is somewhat similar to the sequence for short-term exposures. Figure 2 displays the variety of events which take place during NO_2 exposure. Cell death and replacement predominate during the first two weeks of exposure. Cell replication peaks at approximately two days after exposure initiation. Rate and extent of cell death are dose dependent, just as are other indicators of NO_2-induced damage. A steady state of injury and repair appears to develop after one or two weeks. Concentrations of several blood enzymes increase due to cellular injury after the first week. Susceptibility to infection rises nearly linearly over time due to the increasing destruction of pulmonary defenses. Morphological alterations and pulmonary function changes perhaps require the longest exposure for development. Emphysema-like changes have been demonstrated in experimental animals following extended exposure to relatively low levels of NO_2 (Port, et al., 1977)[29].

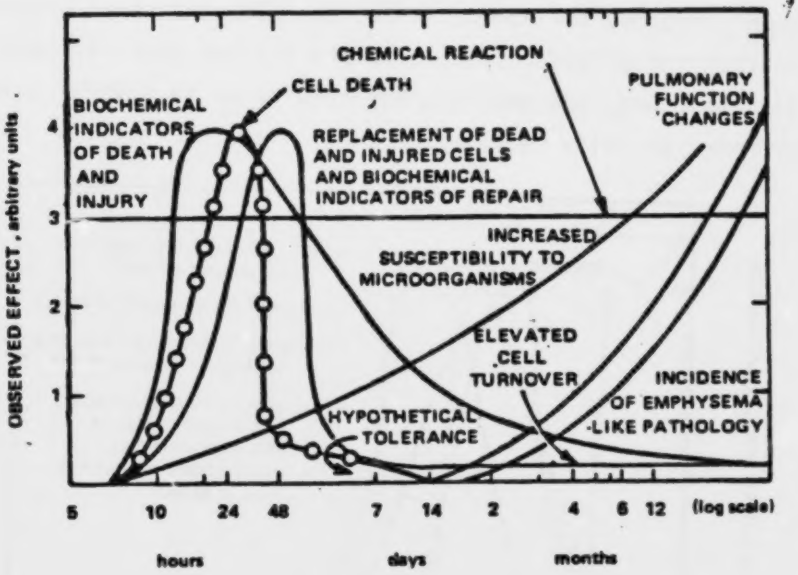


Figure 2. Temporal sequence of injury and repair hypothesized from continuous exposure to NO_2 as observed in experimental animals.[1] (4 on y-axis is equivalent to 100% of Observed Effects)

The influence of exposure mode (concentration x time or C x T) of NO_2 has been investigated in animals, and it has been suggested that, for a constant dose (C x T), brief exposures to high concentrations have a greater effect than prolonged exposures to lower concentrations of NO_2.[11,12,13]

C. Evaluation of Scientific Evidence on Effects Attributed to NO_2 Exposures

A broad spectrum of effects on human and animal respiratory systems has been associated with NO_2 exposure. The time-dependent continuum of observed NO_2 effects ranges from (1) death or irreversible lung damage associated with experimental animal exposures and accidental high exposures of humans in the range of 150-300 ppm or higher; through (2) less severe, but significant short-term and chronic tissue damage, functional impairment, and aggravation of other disease processes at levels of 5-100 ppm; to (3) milder irreversible and reversible effects, such as changes in pulmonary function, which occur at NO_2 levels below 5 ppm.

In reviewing the available scientific data, key animal toxicology studies will be examined to assess what type of effects NO_2 might be expected to cause in humans. Human clinical studies will then be reviewed to identify which effects have been demonstrated to occur in humans. Finally, available epidemiology studies will be reviewed to identify other effects which have been reported to occur in humans. Key among these latter studies are a series of indoor air pollution studies frequently referred to as the "gas stove studies". Throughout the review of the scientific data, primary emphasis will be placed on NO_2 exposures below 5 ppm since concentrations in the ambient air are generally well below this level.

1. Interpretation of Selected Animal Toxicology Studies

Animal toxicology studies can improve the understanding of human health effects of acute and chronic exposures to NO_2. These studies provide health effects information based on scientific endpoints and exposure conditions which would be considered unethical for human chamber studies. Thus, a fuller array of potential effects from NO_2 exposure can be evaluated in animals.

The criteria document contains a review of numerous animal toxicology studies showing a variety of effects in various animal species from exposure to NO_2. In Appendix A of this paper, many of these studies are reviewed and summarized in a manner which facilitates an analysis of the observed health effects. In Table 1 of Appendix A, some of the observed effects from short-term exposure (several hours) are listed. These effects range from very serious and irreversible effects to less serious reversible effects. These effects include: (1) increased mortality from bacterial infection caused by intermittent exposure to 0.5 ppm NO_2 and subsequent exposure to Klebsiella pneumoniae;[14] (2) alveolar damage following repeated (6 hr/day) exposure to 0.5 ppm NO_2;[15] (3) protein in the urine suggestive of kidney damage following multiple 4 hr exposures of 0.4 ppm NO_2;[16] (4) morphological alterations (swollen collagen fibers) following multiple 4 hr/day exposures to 0.25 ppm NO_2;[17] (5) interference with liver metabolism suggested by an increase in pentobarbital-induced sleep time following a single exposure to 0.25 ppm NO_2 for 3 hours;[18] (6) interference with hormone metabolism in the lung following a single exposure to 0.20 ppm NO_2 for 3 hours;[19] and (7) in vivo nitrosamine biosynthesis following exposure to morpholine and a single exposure to 0.20 ppm NO_2 for 4 hours.[20]

In critically assessing animal studies involving short-term exposure to NO_2, it is obvious that numerous effects have been observed for a variety of animal species (dogs, rabbits, guinea pigs, monkeys, rats and mice). There is presently no reliable way to relate human and animal dose-response data. Many of the effects associated with short-term exposures appear to result not from a single exposure, but from multiple exposures in the range of 0.2 ppm to 0.5 ppm for several hours. Of particular interest is that exposure of animals to concentrations slightly above those currently being experienced in the ambient air appears to cause a decrease in resistance to bacterial infection. As will be discussed later, this same type of effect has also been reported to occur in humans.

Table 2 of Appendix A provides a summary of some of the effects which have been associated with animals exposed to NO_2 over relatively long periods (1 day to several years). These effects include: (1) significantly increased susceptibility to infection resulting in increased mortality for continuous and intermittent exposure to $\geq$ 0.5 ppm NO_2;[11-13,21] (2) decreased immunological response resulting in increased respiratory infection for exposures of 0.5-1.0 ppm NO_2, continuous and intermittent;[22,23] (3) increased lung protein content suggesting edema and cell death for 3-6 week exposures to 0.5 or 1.0 ppm NO_2 in Vitamin C deficient animals;[24] (4) hematological disturbances (e.g. increased cholinesterase and lysozyme levels) suggestive of liver[25-27] and heart[25,26] damage at 0.5 ppm NO_2 for 1 week; (5) increased RBC 2,3-diphosphoglycerate, indicating tissue deoxygenation after 1 week exposure to 0.36 ppm NO_2;[28] (6) emphysematous alterations resulting from a six month exposure to 0.1 ppm NO_2 with daily spikes of 1.0 ppm NO_2[29] or 68 months exposure to 0.64 ppm NO_2 and 0.25 ppm NO followed by a 2 year period in clean air.[30]

A critical assessment of the available animal toxicological data for long-term exposure to NO_2 reveals that many of the above effects occur in a variety of animal species, and that many of the effects can be considered serious and irreversible. For example, the emphysematous alterations in dogs associated with long-term exposure to NO_2 are of major concern since the occurrence of this type of effect in humans would clearly be adverse.

While most of the chronic studies were conducted at exposures considerably higher than those encountered in the ambient air, it should be noted that one study[29] did observe emphysematous alterations in mice when exposed to NO_2 levels about twice the current annual standard. However, in this study, the chronic exposure was supplemented with daily spikes of 1.0 ppm and it is not possible to determine if the cause of the effect was chronic exposure, short-term spikes or a combination of these two.

Currently there is no means available to extrapolate the results of the animal studies (either short-term or chronic) directly to humans. Nevertheless, the animal toxicology studies do indicate that NO_2 exposure causes serious biological damage to a number of animals. These studies clearly raise a "warning flag" for potential effects in humans.

2. Review and Evaluation of Controlled Human Exposure with NO_2 Alone

Attention will now be focused on a series of human clinical studies in which humans were exposed to NO_2 in enclosed chambers. We will first discuss those studies in which NO_2 was the sole pollutant present. In a subsequent section similar studies involving simultaneous exposure to NO_2 and other air pollutants will be addressed.

Controlled human exposure studies are valuable in the evaluation of potential health effects related to pollutant exposures because they can provide accurate measurements of exposure levels and conditions for a single pollutant or simple combinations of pollutants. However, clinical studies usually do not provide definitive evidence of effects that might be experienced in the urban environment where exposure levels are constantly changing and multiple pollutants are present in the air. Clinical studies have also been limited to examining the effects of single, short-term exposures and, thus, do not directly address effects that may be caused by repeated, short-term exposures over weeks, months, or longer periods of time.

A number of studies have been conducted which examine effects on healthy adults exposed to single, short-term concentrations of NO_2. A very limited number of clinical studies have tested potentially sensitive subjects such as individuals with asthma or chronic bronchitis. Other groups which may be sensitive to NO_2, such as children or elderly individuals, have yet to be tested in clinical studies for effects that may be due to NO_2 exposure.

Table 1 summarizes reported effects and exposure levels for a selected group of human clinical studies conducted with NO_2 levels at or below 2.0 ppm. These studies have explored four potential indicators of adverse health effects associated with NO_2 exposures: (1) measurable changes in pulmonary function parameters, (2) symptomatic effects (e.g., coughing, chest tightness, etc.), (3) modified response to a pharmacological bronchoconstrictor, and (4) biochemical changes.

a. Pulmonary Function Changes in Adults Exposed to NO_2. The studies summarized in Table 1 and in the Criteria Document (Tables 1-1 and 1-2) indicate that increased airway resistance (R_{aw}) and other physiological

TABLE 1

COMPILATION OF EFFECTS REPORTED IN SELECTED HUMAN STUDIES EXAMINING NITROGEN DIOXIDE EXPOSURES

NO_2 Concentration (ppm)	Exposure Durations	Study Population	Reported Effects	References
0.1	1 hr	20 asthmatics	Specific airway resistance increased and effect of bronchoconstriction enhanced in 13 of 20 subjects after exposure to NO_2. Neither effect observed in 7 of 20 subjects. A bronchoconstrictor (carbachol) was used.	Orehek 1976[38]
0.5	2 hr	10 healthy adults 7 chronic bronchitics 13 asthmatics	1 healthy and 1 bronchitic subject reported slight nasal discharge. 7 asthmatics reported mild symptomatic effects. Bronchitics and asthmatics showed no statistically significant changes for all pulmonary functions tested when analyzed as separate groups; however, small but statistically significant changes in quasi-static compliance were found when analyzed as a single group.	Kerr et al., 1979[32]
0.5 to 5.0	15 min	13 healthy adults 88 chronic bronchitics	Significant decrement in blood gas parameters for both healthy adults and bronchitics. No changes observed below 2.0 ppm.	Von Nieding et al., 1973[37]
0.5 to 5.0	approx. 3 min	63 chronic bronchitics	Significant increase in airway resistance at or above 1.6 ppm.	Von Nieding et al., 1971[36]
0.6	2 hr	15 healthy exercising adults	No physiologically significant changes in cardiovascular, metabolic, or pulmonary function after 15, 30, or 60 minutes of exercise during the 2-hr exposure period.	Folinsbee et al. 1978[34]
0.7 to 2.0	10 min	10 healthy adults	Increased inspiratory and expiratory flow resistance of approximately 50% and 10% of control values measured 10 mins. after exposure.	Suzuki and Ishikawa, 1965[31]
1.0	2 hr	16 healthy adults	No statistically significant changes in pulmonary function tests with exception of small changes in forced vital capacity (1.5% mean decrease; $p < 0.05$). Respiratory symptoms slightly increased after exposure to NO_2, but change not statistically significant compared to controls.	Hackney, 1978[33]
1.0 and 2.5	2 hr	8 healthy adults	Increase in airway resistance at 2.5 ppm but not at 1.0 ppm	Beil and Ulmer, 1976[35]
1.0 and 2.0	2½ hr	10 healthy adults	Alternating exercise and rest produced statistically significant decrease in hemoglobin, hematocrit, and erythrocyte acetycholinesterase.	Posin et al., 1978[39]

changes indicative of impaired pulmonary function have been clearly demonstrated to occur in healthy adults exposed to single 2-hr NO_2 concentrations ranging from 2.5 to 7.0 ppm. Certain studies also indicate statistically significant pulmonary function changes occur in healthy and sensitive subjects after shorter duration exposures (3-10 minutes) to NO_2 concentrations below 2.0 ppm.

In regard to the latter point, Suzuki and Ishikawa (1965)[31] reported increases in inspiratory and expiratory flow resistance of approximately 50 and 10 percent, respectively, over control values for 10 healthy subjects after a 10-minute exposure to NO_2 concentrations in the range of 0.7-2.0 ppm. The authors, however, do not indicate at what point, in this concentration range, effects were first observed, nor do the authors specify whether subjects were exposed to a constant NO_2 level.

Several additional studies of healthy adults[32-35] reported either no statistically significant, or relatively small, changes in pulmonary function at or below 1.0 ppm NO_2. Hackney et al. (1978)[33] reported no statistically significant changes in 18 different measures of pulmonary function with the exception of a marginal loss in forced vital capacity (FVC) (1.5% mean decrease, $p < 0.05$) for 16 healthy adults exposed to 1.0 ppm NO_2 for 2 hours on two successive days. The authors questioned the health significance of this small, but statistically significant, change in FVC in healthy subjects and suggest that the changes found may be due to random variation given the large number of measurements analyzed.

Kerr et al. (1979)[32] exposed 10 normal healthy adults and 20 individuals with asthma and chronic bronchitis to 0.5 ppm NO_2 for 2 hours. A 15-minute period of exercise (light to moderate) was undertaken during the 2-hour exposure. The only statistically significant change reported in a number of pulmonary function measurements examined was in quasistatic compliance in healthy adults and in the group of 20 individuals with asthma and chronic bronchitis. The bronchitics and asthmatics showed no statistically significant changes for all pulmonary functions tested when analyzed as separate groups. The differences reported for the combined group of asthmatics and bronchitics were no larger than the changes reported for a 2-hour period on the first day, which involved no exposure to NO_2. The authors, therefore, suggested that the changes reported may be due to normal daily variation in the subjects rather than to NO_2 exposure. Due to the slight nature of the changes in quasistatic compliance and the absence of statistically significant changes in other pulmonary function measures examined, this study did not demonstrate measurable impairment of pulmonary function in healthy adults or asthmatics and chronic bronchitics exposed for short periods (2 hours) to NO_2 concentrations of 0.5 ppm or below.

Folinsbee et al. (1978)[34] concluded that there were no physiologically significant changes in cardiovascular, metabolic, or pulmonary function for 3 groups of 5 healthy adults where each group underwent a different period of exercise (15, 30, or 60 minutes of light to moderate exercise) and was exposed to 0.6 ppm NO_2 for 2 hours. Similarly, Beil and Ulmer (1976)[35] reported no increase in airway resistance in 8 healthy adults after a 2-hour exposure to 1.0 ppm NO_2. At NO_2 concentrations of 2.5 ppm or above, statistically significant increases in airway resistance were measured by these investigators. However, no statistically significant changes in blood gas parameters (e.g., arterial partial pressure of oxygen and partial pressure of carbon dioxide) were observed.

A limited number of controlled clinical studies have addressed the issue of whether measurable respiratory effects occur in sensitive human subjects exposed to NO_2 levels below 5.0 ppm. Von Nieding et al. (1971)[36] exposed 63 chronic bronchitics to NO_2 concentrations ranging from 0.5 to 5.0 ppm for 30 breaths (approximately 3 minutes). At or below 1.5 ppm no statistically significant changes in pulmonary function were noted. However, at exposure levels of 1.6-2.0 ppm NO_2, statistically significant increases in airway resistance were reported. At levels greater than 2.0 ppm, the increase in airway resistance was more pronounced.

Studies by Von Nieding et al. (1971; 1973)[36,37] also reported that in persons with chronic bronchitis, 10-15 minute exposures to concentrations in the range of 4.0-5.0 ppm produced decreases in arterial partial pressure of oxygen (PaO_2) and increases in the differences between alveolar and arterial blood partial pressure of oxygen ($AaDO_2$). The changes observed in these parameters are indicative of pulmonary function impairment.

b. Symptomatic Effects in Adults Exposed to NO_2. In the Hackney et al. (1978)[33] study, 5 of 16 healthy adult subjects reported an increase in symptomatic effects (cough, chest tightness, laryngitis, and nasal discharge) after exposure to 1.0 ppm NO_2 for 2 hours. However, the difference in symptom scores was not statistically significant over control-group symptom scores. The authors noted that only one of the five sensitive subjects reported chest pain and coughing comparable to typical clinical effects observed in ozone studies. Two others among the five reported lower-respiratory symptoms (coughs or chest tightness), and all five reported upper-respiratory symptoms (nasal discharge or laryngitis). The authors also expressed doubt that the symptom increases were of health significance. Only 1 of 10 healthy subjects in the Kerr et al. (1979) study[32] reported mild symptomatic effects associated with exposure to 0.5 ppm NO_2.

There is evidence that relatively low levels of NO_2 may cause symptomatic effects in individuals with chronic lung disease (i.e., asthmatics and chronic bronchitics). In the Kerr et al. (1979) study[32], 1 of 7 chronic bronchitics and 7 of 13 asthmatics reported various subjective symptoms during or after exposure to 0.5 ppm NO_2 for 2 hours with 15 minutes of light or moderate exercise during the exposure. The authors indicated that the symptoms reported were mild and reversible and included slight headache, nasal discharge, dizziness, chest tightness, and labored breathing during exercise.

c. Effect of NO_2 on Increased Response to a Bronchoconstrictor. The effect of NO_2 on increasing bronchial sensitivity of asthmatic individuals to a bronchoconstricting agent has been investigated by Orehek et al. (1976).[38] The purpose of using a bronchoconstricting agent is to assess possible NO_2 exacerbation of a response that occurs in some asthmatics when they are exposed to agents in the natural environment to which they are particularly sensitive. Orehek obtained dose-response curves for changes in specific airway resistance (SR_{aw}) as a result of subjects inhaling carbachol (a bronchoconstricting agent) after a 1-hour exposure to either clean air or 0.1 ppm NO_2. Only 3 of 20 asthmatics tested showed a marked increase in SR_{aw} following NO_2 exposure; however, when smaller increases in 10 other subjects were combined with the 3 responders there was a small, but statistically significant, increase in SR_{aw} for the group of 13. The NO_2 exposure enhanced the effect of the bronchoconstrictor in the same 13 subjects. Specifically, the mean dose of carbachol producing a twofold increase in SR_{aw} in the 13 sensitive individuals was decreased from 0.77 mg to 0.36 mg as a result of NO_2 exposure. Seven of the asthmatic subjects showed neither an increase in SR_{aw} nor an enhanced effect of carbachol in response to the exposure to NO_2.

The Criteria Document notes that considerable controversy exists over interpretation of the Orehek et al. (1976) study[38] and the health significance of the increased response to a bronchoconstrictor observed in the study. The use of a potent laboratory bronchoconstrictor and selection of a responding group for statistical analysis after the fact make interpretation of this study difficult.

d. Biochemical Changes in Healthy Adults Exposed to NO_2. A single study by Posin et al. (1978)[39] reported statistically significant decreases in hemoglobin, hematocrit, and erythrocyte acetylcholinesterase in 10 healthy subjects who were exposed to 1.0 ppm NO_2 for 2.5 hours. Other blood biochemical changes, such as elevated levels of red blood cell lipids, were reported after exposure to 2.0 ppm. Some questions have been raised as to the importance of these findings due to considerable day to day variability in the physiological parameters that were measured in the absence of NO_2 exposures.

e. Staff Comments on Controlled Human Exposure Studies (NO_2 Alone) Due to a paucity of controlled human studies involving healthy individuals and particularly more susceptible members of the population, there is considerable uncertainty about the lowest exposure levels of NO_2 that will cause (1) measurable impairment of pulmonary function, (2) symptomatic effects, (3) increased responsiveness to bronchoconstricting agents in the environment, or (4) biochemical changes.

With regard to the lowest level of NO_2 associated with measurable impairment of pulmonary function, most studies[32-35] involving exposures in the range of 0.5 to 1.5 have reported little or no change in pulmonary function. The possible exception is the Suzuki and Ishikawa study,[31] which reported statistically significant changes in inspiratory and expiratory flow resistance in 10 healthy adults after a 10-minute exposure to NO_2 concentrations somewhere in the range 0.7-2.0 ppm. It is not possible, however, to identify the specific concentration(s) within the range that was associated with the observed effects. However, the fact that Hackney et al. (1978)[33] and Beil and Ulmer (1976)[35] reported no statistically significant changes in pulmonary function after 2-hour exposures to 1.0 ppm NO_2 suggests that the effects observed by Suzuki and Ishikawa were probably associated with NO_2 concentrations above 1.0 ppm.

The Von Nieding et al. (1971)[36] study provides convincing evidence that chronic bronchitics exposed to NO_2 concentrations of 1.6 ppm or greater for approximately 3 minutes experience increases in airway resistance. Based on a review of the available evidence, the lowest level of NO_2 exposure that credible studies have associated with measurable impairment of pulmonary function appears to be in the range 1.0 - 1.6 ppm.

It should be noted that the exposure periods were considerably less than 1 hour in two of the studies[31,36] reporting pulmonary function changes. The health significance, however, of the small changes in pulmonary function reported in these two studies is uncertain. Several CASAC members have expressed concern that a standard designed to prevent relatively small changes in pulmonary function (such as those observed in the Suzuki and Ishikawa[31] and Von Nieding et al.[36] studies) from occurring more than once per year would be unneccessarily stringent.[4] The CASAC members indicated that they were more concerned about the health implications of repeated exposures to the peak concentrations observed in the two studies than the effects associated with a single exposure.

A judgment that must be made with regard to the above evidence concerns the degree of change in pulmonary function that should be considered an adverse health effect. Because the human respiratory system is endowed with a large reserve capacity, fairly large changes in pulmonary function (e.g., 50 percent increase in airway resistance) may not ordinarily be perceived in normal, healthy adults. However, a portion of the population with respiratory problems may be operating at or near the limit of their lung function capacity when engaged in light or moderate exercise. For these individuals, a relatively small impairment of lung function may affect their ability to perform certain tasks or may aggravate a pre-existing pulmonary disease.

Another area of uncertainty concerns the lowest levels of NO_2 exposure that will lead to symptomatic effects in healthy adults and sensitive individuals. As indicated above, only very limited data are available from a relatively small number of subjects. The available evidence suggests that few, if any, healthy adults would experience discomfort or other subjective symptoms during or after short-term (less than 2-hr) exposures to NO_2 concentrations at or below 1.0 ppm. The evidence from the Kerr et al. (1979) study[32] indicates that some sensitive individuals (particularly asthmatics) may experience mild and reversible symptomatic effects, such as wheezing and chest tightness, upon exposure to 0.5 ppm NO_2 for 2 hours.

The symptomatic effects observed in asthmatics are of concern because they cause discomfort and may restrict normal activity or limit the performance of tasks. There is also concern, based on reasonable medical judgment or hypothesis, that the symptomatic effects observed may be indicators of other deleterious effects occurring in the respiratory system which currently cannot be measured in human studies due to ethical limits on testing and limitations of current measurement technique. Therefore, although these symptoms appear to be reversible and transitory we are concerned that symptomatic effects, such as those observed in the Kerr et al. (1979) study[32] after exposure to 0.5 ppm NO_2 for 2 hours with intermittent exercise, may constitute adverse health effects for some individuals. If these symptomatic effects are not judged by the Administrator to be adverse health effects within the guidance provided by the Clean Air Act and its legislative history, they still may be considered as a factor in judging which standard would provide an adequate margin of safety and/or be considered in setting a short-term secondary standard for NO_2.

With regard to possible increased responsiveness of asthmatics to bronchoconstricting agents in the environment, the results of the Orehek study are inconclusive. Due to the small magnitude of the responses, lack of reported symptoms in the subjects, and selection of responders after the fact in the Orehek study, it remains to be determined which levels of NO_2 may produce significant effects in asthmatics under ambient exposure conditions although it provides suggestive evidence that asthmatics may respond to NO_2 at lower levels than healthy persons.

3. Review and Evaluation of Controlled Human Exposure Studies with NO_2 and Other Pollutants

a. Reported Findings. It has been theorized that concurrent exposure to multiple pollutants might produce additive or greater than additive health effects. This has been investigated in several studies involving NO_2 and other pollutants such as ozone (O_3), carbon monoxide (CO), and sulfur dioxide (SO_2). Table 2 summarizes the reported findings and exposure levels for these studies.

Several investigations involving multiple pollutant exposures have failed to find any additional effects due to the addition of NO_2 beyond those found for O_3 alone. Hackney et al. (1975)[40,41] reported little or no change in pulmonary function measurements (FVC, FEV, R_{aw}, and others) in healthy volunteers exposed to NO_2 and other pollutants concurrently. Four healthy subjects exposed to 0.5 ppm O_3; to O_3 and 0.3 ppm NO_2; and to O_3, NO_2 and 30 ppm CO showed no increase in pulmonary function beyond minimal alterations which were observed for subjects exposed to O_3 alone.[40] Another group of 7 subjects, including some thought to be unusually reactive to irritants, showed little or no change in pulmonary function following a 2-hour exposure to 0.25 ppm O_3 alone, or with addition of 0.3 ppm NO_2 or NO_2 plus 30 ppm CO.[41] Finally, Horvath and Folinsbee (1979)[42] found no additive effects or interaction between 0.5 ppm O_3 plus 0.5 ppm NO_2 under four different environmental conditions involving changes in temperature and relative humidity.

Von Nieding et al. (1977)[43] reported no changes in R_{aw} or difference between alveolar and arterial blood partial pressure of oxygen ($AaDO_2$) in 11 healthy subjects exposed to 0.05 ppm NO_2, 0.025 ppm O_3, and 0.11 ppm SO_2 for 2 hours. Nine of these healthy subjects were exposed to the same mixture of pollutants followed by bronchial challenges involving inhalation of an aerosol containing 1%, 2%, and 3% acetylcholine. A statistically significant increase in specific resistance relative to the control exposure ($p < 0.1$) was reported for the 2% acetylcholine solution. The increases in specific resistance with the 1% and 3% acetylcholine solutions and mixture of pollutants, however, were not statistically significant. The

TABLE 2

EFFECTS ON PULMONARY FUNCTION IN SUBJECTS EXPOSED TO NO_2 AND OTHER POLLUTANTS

Concentration (ppm)	Exposure Duration	Study Population	Reported Effects	References
$0.05\ NO_2 + .11\ SO_2 + 0.025\ O_3$	2-Hours	11 healthy subjects	Increased sensitivity to bronchoconstrictor as shown by increases in R_{aw}. No effect on A_aDO_2 or R_{aw} without bronchoconstrictor.	von Nieding et al., 1977[43]
$0.50\ O_3$; $0.50\ O_3 + 0.29\ NO_2$; $0.50\ O_3 + .29\ NO_2 + 30\ CO$	4-Hours	4 healthy male subjects	Minimal change in pulmonary function caused by O_3 alone. Effects not caused by NO_2 or CO.	Hackney et al., 1975[41]
$0.25\ O_3$; $0.25\ O_3 + 0.29\ NO_2$; $0.25\ O_3 + 0.29\ NO_2 + 30\ CO$	2-Hours	7 male subjects, some believed to be unusually reactive to respiratory irritants	Minimal change in pulmonary function caused by O_3 alone. Effects not increased by NO_2 or CO.	Hackney et al., 1975[40]
$50\ CO + 5\ SO_2$; $4.8\ NO_2 + 50\ CO + 5\ SO_2$	-	3 subjects	Increase in dust retention from 50% to 76% after NO_2 was added to air containing SO_2 and CO.	Schlipköter and Brockhaus, 1963[45]
$0.5\ O_3$; $0.5\ O_3 + 0.5\ NO_2$ UNDER FOLLOWING CONDITIONS: 1) 25°C, 45% rh 2) 30°C, 85% rh 3) 35°C, 40% rh 4) 40°C, 50% rh	Rest-60 min. Exercise-30 min. Rest-30 min.	8 young adults	Response found only for O_3; no greater than additive effect or interaction between O_3 and NO_2 was observed.	Horvath and Folinsbee, 1979[42]

nine healthy subjects were also exposed to a mixture containing 5 ppm NO_2, 0.1 ppm O_3, and 5 ppm SO_2 followed by the same bronchial challenges noted above. The authors observed a more pronounced response which was statistically significant for all three acetylcholine concentrations ($p < 0.01$). Some of the methods used by Von Nieding and his co-workers differ from those used in the United States and may not be directly comparable. In spite of the differences in techniques, it is generally agreed that the methods used by Von Nieding provide valid information on directional changes in R_{aw} or $AaDO_2$.[44]

Schlipköter and Brockhaus (1963)[45] studied the effects of exposure to 4.8 ppm NO_2, 50 ppm CO, and 5 ppm SO_2 on lung deposition of inhaled dusts (0.07 to 1.0 micrometers). Under control conditions and with CO and SO_2 exposures, 50 percent of the dust was retained. Dust retention increased to 76 percent when dust was administered in an atmosphere containing 4.8 ppm NO_2 along with 50 ppm CO and 5 ppm SO_2. This study suggests that elevated NO_2 concentrations in inhaled air may result in retention of larger proportions of inhaled particulate matter; but specific dose-effect relationships for the induction of such effects remain to be determined.

b. Staff Comment on Controlled Human Exposure Studies (NO_2 with Other Pollutants). The studies discussed above provide little support for additive or greater-than-additive effects being associated with exposure to ambient concentrations of NO_2 in the presence of other pollutants such as O_3, CO, or SO_2. The principal exception is the increase in sensitivity to a bronchoconstrictor (acetylcholine) after exposure to a mixture containing NO_2, O_3, and SO_2 reported by Von Nieding et al. (1977).[43] The Criteria Document explains the difficulty in interpreting Von Nieding's findings in view of: (1) the uncertain health significance of altered sensitivity to bronchoconstrictors in healthy or sensitive subjects; (2) some uncertainties due to methodological differences between his techniques and other investigators; and (3) lack of confirmation of the findings by other investigators.[46] Due to the concerns stated above, the results of the Von Nieding study should not be used in determining the lowest concentration convincingly associated with adverse health effects. The study should be considered solely as a factor in judging which standard(s) will provide an adequate margin of safety.

4. Review and Evaluation of Selected Community Epidemiological Studies

a. Reported Findings. Interpretation of epidemiological studies on the effects of individual air pollutants is unavoidably complicated by the complex mixtures of pollutants in air. The most that can usually be demonstrated by such studies is an association, and not a cause and effect relationship between health effects and ambient concentrations of a given pollutant. Epidemiological studies have often been hampered by methodological problems and the resultant difficulties in determining actual exposures for study populations. The major advantage of epidemiological evidence is that it reflects real world exposures to the pollutant along with exposure to other pollutants and environmental stresses (e.g., temperature, humidity, etc.).

Community studies on the effects of NO_2 exposure conducted prior to 1973 are of questionable validity due to the use of the Jacobs-Hocheiser method of measuring atmospheric concentrations of NO_2. This method has since been withdrawn, and studies which used the Jacobs-Hocheiser method are of limited value because quantitative NO_2 exposure levels cannot be reliably determined.

Shy et al.[47,48] have reported small, but statistically significant, decreases in FEV in children (7 to 8 years old) living in areas of relatively high NO_2 concentrations compared to children living in areas with lower NO_2 concentrations. Studies by Shy and co-workers[47-49] also suggested that the incidence of acute respiratory disease during 1968-69 was 19 percent higher for families living in apparently high NO_2 exposure areas of Chattanooga than for control families in apparently lower NO_2 exposure areas. The distances of three study communities from a large point source of NO_2 (a TNT plant which is no longer in operation) resulted in an apparent gradient of exposure over which illness rates were determined. However, the studies [47-49] conducted by Shy and co-workers in 1968-69 in Chattanooga, which in part formed the basis for the existing annual NO_2 standard, cannot be used to determine quantitative relationships between NO_2 levels and specific health effects due to the problems with the measurement of NO_2 levels. Shy's follow-up study[50] of lung function in school children conducted during the 1971-72 school year failed to report any noticeable pulmonary function deficits. It should be noted that ambient NO_2 levels were lower in 1971-72 due to the shutdown of the large NO_x point source in Chattanooga.

In a retrospective study in Chattanooga, Pearlman et al. (1971)[49] studied respiratory disease among first- and second-grade school children and among children born between 1966-68. The Criteria Document states that from among several respiratory disease indicators assessed, only some bronchitis rates in children were reported to be higher in the area of maximum NO_2 concentration; no significant differences were seen for bronchitis rates for children living in the study areas for 1 or 2 years. The bronchitis rates for children who had lived in the same neighborhood for 3 or more years were reported to be significantly greater (32.2 per 100) than those for children in the low concentration area (23.2 per 100). According to the Criteria Document, however, health survey instrument validation results indicated somewhat questionable accuracy of parental recall of whether bronchitis episodes occurred before or after moving into study areas 3 years earlier. Clear-cut estimates of NO_2 exposure levels associated with reported health effects are not available.

Other community epidemiology studies which have often been cited regarding NO_2 are summarized in Table 3. While most of these studies tend to indicate that reported concentrations of NO_2 had no detectable effects on lung function, an exception is the Kagawa and Toyama (1975) study[51] which showed some correlation between maximum expiratory flow rate or specific airway conductance and NO_2 levels at the time of the study. One-hour NO_2 concentrations were measured once a day during the study and ranged from 0.02 to 0.19 ppm, but the data do not allow quantitative estimation of specific NO_2 levels that might have been associated with the occurrence of pulmonary function decrements. Nor do the results allow one to discern clearly the relative contribution of NO_2 to induction of observed respiratory effects versus those due to a complex interaction of pollutants including NO_2.

Linn et al. (1976),[52] Cohen et al. (1972),[53] Burgess et al. (1973),[54] and Speizer and Ferris (1973a,b)[55,56] found no differences in pulmonary function tests in separate epidemiological studies which also involved complex pollutant mixtures in ambient air. The NO_2 concentrations were in the range 0.02-0.51 ppm in these epidemiological studies.

b. Staff Comments on Community Epidemiology Studies. Due to methodological problems (i.e., use of Jacob-Hocheiser method) with the Shy et al.[47,48,50] and Pearlman et al.[49] studies performed in Chattanooga, derivation of a quantitative assessment of the health effects reported to be

TABLE 3

EFFECTS OF EXPOSURE TO NO$_2$ ON PULMONARY FUNCTION IN COMMUNITY EPIDEMIOLOGY STUDIES

Exposure Concentrations (ppm)	Study Population	Reported Effects	References
Median hourly 0.07 NO$_2$ Median hourly 0.15 O$_x$ Median hourly 0.35 NO$_2$ Median hourly 0.02 O$_x$	205 office workers in L.A. 439 office workers in San Francisco	No differences in most tests. Smokers in both cities showed greater changes in pulmonary function than non-smokers.	Linn et al., 1976 [52]
High exposure area 24 hr high 0.055 NO$_2$ .035 SO$_2$ 1-hr mean High exposure area 0.14 NO$_2$ to 0.30 NO$_2$ Low exposure area 0.06 NO$_2$ to 0.09 NO$_2$	128 traffic policemen in urban Boston and 140 patrol officers in nearby suburbs	No dif'erence in various pulmonary function tests	Speizer and Ferris, 1973 [55] Burgess et al. 1973 [54]
High exposure group: Estimated 1-hr max 0.26 to 0.51 NO$_2$ Annual mean 24-hr 0.051 NO$_2$ Low Exposure groups: Estimated 1 hr max 0.12 to 0.23 NO$_2$ Annual mean 24 hr 0.01 NO$_2$	Nonsmokers in L.A. (adult)	No differences found in several ventilatory measurements including spirometry and flow volume curves	Cohen et al., 1972 [53]
1 hr conc. at time of testing (1:00 p.m.) 0.02 to 0.19 NO$_2$	20 school age children 11 years of age	During warmer part of year, NO$_2$, SO$_2$, and TSP significantly correlated with V_{max} at 25% & 50% FVC specific airway conductance. Significant correlation between each of four pollutants (NO$_2$, NO, SO$_2$ and TSP) and V_{max} at 25% and 50% FVC; but no clear delineation of specific pollutant concentrations at which effects occur.	Kagawa and Toyama, 1975 [51]

associated with NO_2 levels from these studies is not possible. There is also considerable difficulty in trying to sort out any health effects caused by NO_2 from effects caused by other pollutants found in the ambient air (e.g., ozone, particulates, SO_2) at the time of the study. In our judgment, these problems severely limit the usefulness of these studies for standard-setting purposes.

While the Kagawa and Toyama study[51] shows some pulmonary function effects related to NO_2 concentration, the results suggest that the observed respiratory effects are caused by a complex mixture of pollutants. Also, inadequate characterization of exposure to NO_2 prevents our drawing any firm conclusions about the relationship between NO_2 exposure and resulting health effects.

At best we can only conclude that the findings of Shy et al.,[47,48,50] Pearlman et al.,[49] and Kagawa and Toyama[51] are not inconsistent with the hypothesis that NO_2, in a complex mix with other pollutants in the ambient air, adversely affects respiratory function and illness in children. That is, although these studies do not provide clear evidence for positive associations between health effects and ambient exposures to NO_2, neither do they suggest that negative or no associations exist between such variables. Little or no evidence of health effects at ambient concentrations of NO_2 is provided by other community epidemiological studies.

It should be recognized that the community epidemiology studies cited and discussed above did not take into account exposure to, and effects of, indoor air pollutants, such as NO_2 generated by the use of gas stoves. The next section focuses on evidence of health effects associated with exposure to NO_2 concentrations indoors.

5. Review and Evaluation of Epidemiological Studies Involving Homes with Gas Stoves

A number of epidemiological studies have been conducted in the United States and Great Britain which investigate the effects of indoor air pollution on individuals living in homes with gas stoves compared to those living in homes with electric stoves. Since several investigators have found significantly higher levels of NO_2 in gas stove versus electric stove homes, these studies provide an opportunity to explore the potential health impacts of repeated short-term peaks and long-term exposures of NO_2 on children and adults. The principal studies investigating indoor air pollution in gas stove homes are summarized in Table 4.

TABLE 4

COMPILATION OF REPORTED EFFECTS ASSOCIATED WITH EXPOSURE TO NO_2 IN THE HOME IN COMMUNITY STUDIES INVOLVING GAS STOVES[a]

NO_2 Concentration (ppm)	Study Population	Reported Effects [b]	References
95th percentile of 24 hr avg in activity room 0.02 - 0.06 (gas) 0.01 - 0.05 (elec.) Frequent peaks in 1 home of 0.4-0.6 (gas). Maximum peak 1.0 (gas).	8,120 children, ages 6-10, 6 different cities, data also collected on history of illness before age 2	Significant association between history of serious respiratory illness before age 2 and use of gas stoves ($p < .01$). Also, small but statistically significant decreases in pulmonary function (FEV_1 and FVC) in children from gas stove homes.	Speizer et al., 1980 55
NO_2 concentrations not measured at time of study.	2,554 children from homes using gas to cook compared to 3,204 children from homes using electricity, ages 6-11	Proportion of children with one or more respiratory symptoms or disease (bronchitis, day or night cough, morning cough, cold going to chest, wheeze, asthma) increased in homes with gas stoves vs. electric stove homes (for girls $p \simeq 0.10$; boys not sig.) after controlling for confounding factors.	Melia et al., 1977 57
NO_2 concentrations not measured in some homes studied for health effects.	4827 children, ages 5-10	Higher incidence of respiratory symptoms and disease associated with gas stoves (for boys $p \simeq 0.02$; girls $p \simeq 0.15$) for residences in urban but not rural areas, after controlling for confounding factors.	Melia et al., 1979 58
Kitchens (weekly avg.): 0.005-0.317 (gas) 0.006-0.188 (elec.) Bedrooms (weekly avg.): 0.004-0.169 (gas) 0.003-0.037 (elec.)	808 children, ages 6-7	Higher incidence of respiratory illness in gas-stove homes ($p \simeq 0.10$). Prevalence not related to kitchen NO_2 levels, but increased with NO_2 levels in bedrooms of children in gas-stove homes. Lung function not related to NO_2 levels in kitchen or bedroom.	Florey et al., 1979 60 and Goldstein et al., 1979 59 (both are companion papers to Melia et al., 1979)
Sample of households 24 hr. avg: 0.005-0.11 (gas) 0-0.06 (elec.) 0.015-0.05 (outdoors)	128 children, ages 0-5 346 children, ages 6-10 421 children, ages 11-15	No significant difference in reported respiratory illness between homes with gas and electric stoves in children from birth to 12 years.	Mitchell et al., 1974 67 See also Keller et al., 1979 68
Sample of household same as reported above but in no new monitoring reported.	174 children under 12	No evidence that cooking mode is associated with the incidence of acute respiratory illness.	Keller et al., 1979 68
See above for monitoring.	Housewives cooking with gas stoves, compared to those cooking with electric stoves. 146 households.	No evidence that cooking with gas associated with an increase in respiratory disease.	Keller et al., 1979 68
See above for monitoring.	Members of 441 households	No significant difference in reported respiratory illness among adults in gas vs electric cooking homes.	Mitchell et al., 1974 67 See also Keller et al., 1979a 68
Preliminary measurements peak hourly .25-0.50, max. 1.0	Housewives cooking with gas stoves, compared to those cooking with electric stoves	No increased respiratory illness associated with gas stove usage.	U.S. EPA, 1976

[a] Exposures in gas stove homes were to NO_2 plus other gas combustion products.

[b] Effects reported in published references are summarized here. However, the Criteria Document warns that considerable caution should be used in drawing firm conclusions from these studies.

a. Increased Incidence of Acute Respiratory Illness and Symptoms in Children Living in Gas Stove Homes - Reported Findings. Two groups of investigators, one in Great Britain and one in the United States, have reported increases in respiratory illness and/or respiratory symptoms in children living in homes which used gas stoves for cooking compared to children living in homes which used electric stoves. Results of the British study have been reported by Melia et al. (1977, 1979)[57,58], Goldstein et al. (1979)[59], and Florey et al. (1979).[60] The initial study, conducted from 1973 to 1977, investigated the effects of indoor and outdoor air pollution on respiratory illness and symptoms in a large group of young school children from randomly selected areas in England and Scotland.

Melia et al. (1977)[57] reported that cross-sectional analysis of the 1973 results indicated that crude prevalences of bronchitis, cough, colds going to the chest, wheeze, and asthma were higher in children ages 6-11 living in gas stove homes. The increases in prevalence were statistically significant ($p < 0.05$) for bronchitis, cough, and colds going to the chest in both sexes, and for wheeze in girls. For bronchitis, the prevalence in gas stove homes was 5.7 and 4.7 percent for boys and girls, respectively, compared to 3.1 and 2.0 percent for boys and girls living in electric stove homes. The authors reported that the observed effect appeared to be independent of a number of possibly confounding factors, including age, social class, latitude, population density, family size, outdoor levels of smoke and sulfur dioxide, and home heating fuel. This conclusion was based on the proportion of children with one or more diseases or symptoms being higher for gas stove homes when these various factors were taken into account. However, when all of the factors were considered, the proportion of children with one or more symptoms or diseases remaining higher only approached significance for girls ($p \underset{-}{\sim} 0.10$) but not boys. It should be noted that the data for 1973 did not include smoking habits of family members which may have contributed to the effects observed (see Tager et al., 1979).[61]

Melia et al. (1979)[58] reported the results of a similar cross-sectional analysis for a different set of children studied in 1977. The authors found crude prevalences of cough in boys ($p \underset{-}{\sim} 0.02$) and colds going to the chest in girls ($p < 0.05$) were significantly higher in homes with gas stoves. When prevalences of the respiratory conditions reported in the 1973 study were grouped, an association of gas cooking with occurrence of one or more symptoms was found in both sexes ($p \simeq 0.01$ in boys, $p \simeq 0.07$ in girls). When possible confounding factors considered in 1973, plus smoking among family members, were taken into account, an association between gas cooking and respiratory conditions was found in urban areas ($p < 0.005$ in boys, $p \simeq 0.08$ in girls) but not in rural ones.

A major difficulty in interpreting the results from the two Melia et al. studies described above is the lack of air pollutant measurements in the specific residences of the subjects studied. In a separate study, Melia et al. (1978)[62] have reported higher NO_2 concentrations in the kitchens of two gas stove homes compared to two electric homes. The average hourly concentration of NO_2 in gas kitchens was 0.072 ppm, compared to 0.009 ppm in the electric kitchens.

The Melia et al. studies[57,58] appear to provide some suggestive evidence for an association between exposure to gas stove combustion products and increased incidence of acute respiratory symptoms and illness in children. However, the authors of the Melia et al. studies have expressed concern that the effects observed in their study may be due to some factors other than NO_2, such as increased water vapor in gas stove homes. No information is available, however, to confirm or refute the possible contribution of other factors, such as increased humidity, to increases in respiratory illness and symptoms.

Due to the incomplete analysis of possible confounding or covarying factors (e.g., temperature and humidity) and the lack of short-term NO_2 measurements in the homes of the subjects studied, only the above qualitative conclusions may be drawn regarding the Melia et al. studies.

In related research, a group of British investigators have studied further the possible impact of NO_2 exposures in gas stove homes on increased respiratory infection and decreased lung function. Goldstein et al. (1979)[59] and Florey et al. (1979)[60] reported higher prevalence of respiratory symptoms for children in gas stove homes than in electric stove homes ($p \simeq 0.10$). The study[59] reported that weekly mean NO_2 concentrations in 428 kitchens with gas stoves ranged from 0.005-0.317 ppm (mean 0.112 ppm) compared to weekly mean levels from 0.006-0.188 ppm (mean 0.018 ppm) in 87 kitchens where electricity was used for cooking. The weekly mean NO_2 levels were 0.02 ppm or greater in all but one gas stove home, while only 11 of the 87 (12.6%) electric stove homes had weekly mean concentrations of 0.02 ppm or higher. When various confounding factors were considered, the study found only a weak association between prevalence of respiratory illness in 6- to 7-year old children and gas cooking in their homes. Lung function tests also were performed on the children, but no statistically significant associations were found between lung function and NO_2 concentrations in the kitchens or bedrooms.

Speizer et al. (1980)[64] and Spengler et al. (1979)[65] have reported results from an ongoing prospective epidemiological study of six communities in the United States. They reported, based on a questionnaire completed by parents, a statistically significant increase in respiratory illness in their children before age 2. The study also reported a slight decrease in pulmonary function, based on actual measurements, for children 6 to 9 years of age who were living in homes where gas was used for cooking.

The rate of acute respiratory illness in children before the age of 2, adjusted for parental smoking, social class, and city-cohort, was reported as 32.5/1000 higher in gas stove homes than in electric stove homes. This is an increase of between 16 and 26% compared with the 127 to 204/1000 rates observed in the electric stove homes. The authors have recently indicated their concern that further analysis of data from their study be conducted to confirm if differences in socio-economic status were a major factor associated with the reported increase in rate of respiratory illness before age 2.

Speizer et al. (1980)[64] also reported lower pulmonary function levels in children 6 to 9 years of age who lived in gas stove homes. The changes in two pulmonary function measures (FEV_1 and FVC) were small (average difference 17 ml and 18 ml, respectively) but statistically significant compared to children living in electric stove homes. The authors hypothesize that the decrements in pulmonary function measurements observed may be an indicator that the lungs of some of these children may not reach their full adult lung size. Further, the authors present a biologically plausible hypothesis that persons with minor impairment of total lung growth may be more susceptible to developing respiratory problems during their adult life.[64]

The Speizer et al. study[64] monitored 24-hour average concentrations over a 1-year period in the "activity room" (but not the kitchen) of several (5-11) electric and gas stove homes in each of the six communities studied. The monitoring results show that 24-hour average concentrations in electric stove homes approximate levels monitored outside these homes. An increase in NO_2 levels was observed in homes with gas stoves in five of the six communities, which reflects the addition of indoor sources to outdoor levels of NO_2. The 95th percentile of measured indoor 24-hour average NO_2 concentrations for homes in 6 cities were reported to be in the range of 0.02-0.06 ppm for gas stove homes and 0.01-0.05 ppm for electric stove homes. The measurement method employed to obtain 24-hour average levels was the Saltzman (sodium arsenite) - bubbler method. The authors of the study have indicated that the carbon dioxide (CO_2) levels expected indoors may have interfered with the NO_2 measurements, resulting in lower NO_2 levels being recorded than actually occurred.[66]

As part of the same Six-City Study, Spengler et al. (1979)[65] monitored NO_2 levels in one kitchen of a gas stove home for approximately 2 weeks. Short-term peaks in excess of 0.25 ppm, and even 0.5 ppm NO_2, which lasted from minutes to hours, were measured in the kitchen during cooking. The complete data set from the Spengler et al. (1979)[65] study are not available and, therefore, EPA is unable to characterize the frequency distribution of short-term peak NO_2 levels based on this study. Other studies, unrelated to the Six-City Study have monitored NO_2 concentrations in gas stove homes under a variety of conditions. The results of these studies are summarized and discussed in the next section (Analysis of NO_2 Levels in Gas and Electric Stove Homes).

A series of studies by another group of investigators, Mitchell et al. (1974)[67] and Keller et al. (1979),[68] found no association between the use of gas stoves and increased rates of respiratory disease in either children or adults. However, the number of children used in these studies was approximately a factor of 10 smaller than in both the British and U.S. studies, which yielded an association between increased prevalence of respiratory illness and gas cooking. The relatively small sample size would tend to lessen the likelihood of these studies finding statistically significant differences, since the main health effect being investigated is a relatively small difference in disease and symptom prevalence rates.

b. Analysis of NO_2 Levels in Gas and Electric Stove Homes. Since the Six-City Study, to date, has not monitored short-term NO_2 levels sufficiently, it is necessary to examine other studies which have monitored NO_2 levels in other gas stove homes in order to estimate NO_2 levels that may have occured in the Six-City Study homes. Table 5 summarizes the available data on NO_2 levels in U.S. homes and in experimental buildings.

The study with the greatest amount of data on short-term NO_2 levels in a variety of gas stove houses is reported in Wade et al. (1975)[69] and Cote et al. (1974)[70]. They monitored NO_2 levels in 4 houses in a suburban community in Connecticut using a chemiluminescent analyzer. Five minute samples were generally taken 6 times during each 2-hour interval and accumulated into 2-hour averages. Approximately two weeks of monitoring were performed at each of four gas stove homes during the spring and summer of 1973 and the fall and winter of 1973-1974. Values for Home 2 were not summarized in Table 5, because the home was occupied by a young bachelor who rarely used the stove; thus, the home tended to show the same levels of NO_2 that were found outside.

The mean daily 2-hour peak in the kitchen of 3 of the homes ranged from 0.10-0.18 ppm NO_2. During the study, the occupants of the home kept a diary of stove use. Comparing these diaries of stove use and occurrence of peak NO_2 concentrations, one can conclude that the peak levels in the kitchen and living room were directly related to use of the gas stove and

TABLE 5

NITROGEN DIOXIDE LEVELS REPORTED IN GAS AND ELECTRIC STOVE HOMES

Study	Site and Conditions	Parameter	NO_2 Concentration (ppm)			Measurement Method
			Home 1: 2000 ft. split-level with well ventilated kitchen.	Home 3: 2-story apartment with small, unventilated kitchen.	Home 4: 1500 ft^2 ranch style with kitchen open to other areas of house.	
			range (mean)	range (mean)	range (mean)	
Cote, Wade, and Yocom, 1974.[70]	Kitchen, 1 meter from stove	Daily peak 2-hr avg 24-hr avg	0.04-.28 (.10) 0.01-.08 (.04)	.03-.31 (.10) .03-.13 (.06)	.05-.41 (.18) .04-.11 (.06)	Chemiluminesent Analyzer
Suburban homes In Connecticut.	Living room	Daily peak 2-hr avg 24-hr avg	0.01-.17 (.06) 0.01-.05 (.03)	.01-.06 (.04) .01-.04 (.03)	.04-.35 (.11) .03-.07 (.04)	
	Bedroom	Daily peak 2-hr avg 24-hr avg	0.02-.09 (.05) 0.02-.04 (.03)	.02-.19 (.07) .03-.05 (.03)		
	Outdoors	Daily peak 2-hr avg 24-hr avg	0.02-.08 (.04) 0.01-.05 (.02)	.01-.09 (.04) .02-.03 (.02)	.02-.12 (.05) .01-.04 (.02)	

(Table continued on next page)

TABLE 5 (Con't)

NITROGEN DIOXIDE LEVELS REPORTED IN GAS AND ELECTRIC STOVE HOMES

Study	Site and Conditions	Parameter	NO_2 Concentration (ppm)	Measurement Method
Hollowel et al., 1980[71]				Chemilumi-nesent Analyzer
Energy efficient research house, .33-.44 air changes per hour (ach).	Study simulated typical gas stove use patterns			
	Kitchen	Peak 1-hr avg 24-hr avg	0.45 0.07	
	Living room	Peak 1-hr avg 24-hr avg	0.40 0.07	
	Bedroom	Peak 1-hr avg 24-hr avg	0.24 0.05	
	Outdoors	Peak 1-hr avg 24-hr avg	0.07 0.04	
Hollowel et al.,[illegible] 1978.	Kitchen with a gas oven on for 1-hr @ 350°F			Chemiluminescent Analyzer
Test kitchen ($27m^3$)	0.25 ach (no stove vent)	1-hr average	1.20	
	1.0 ach (hood vent above stove)	1-hr average	0.80	
	2.5 ach (hood vent with fan at 50 CFM)	1-hr average	0.40	
	7.0 ach (hood vent with fan at 140 CFM)	1-hr average	0.10	
	Outside during test	1-hr average	0.03	
Keller et al.,[68] 1979.			range (mean)	Modified Jacobs-Hochheiser (arsenite modified)
Gas and electric stove homes in Columbus, Ohio	83 gas stove homes	24-hr average	0.01-.11 (0.05)	
	50 electric stove homes	24-hr average	0-.06 (.02)	
	53 outdoor samples in vicinity	24-hr average	0.02-.05 (.03)	
	46 gas stove	continuous measurement over 3 day periods	peak values in some homes exceeded 1 ppm; peaks during cooking reached as high as 8 times the 24-hr average	Chemiluminescent Analyzer
Speizer et al.,[55] 1980. Activity room in 5-11 gas and electric stove homes in each of six communities. Also monitored in 1 kitchen of a gas stove home for 2 weeks.	Activity room (gas stove homes)	95th percentile of 24-hr averages measured over a 1 year period	0.02-.06	Modified Sodium Arsenite
	Activity room (electric stove homes)		0.01-.05	
	Outdoors		0.01-.06	
	Kitchen, 3-feet from gas stove homes	continuous	peak concentrations in the range of 0.25-0.50 were observed for 10-15 minute periods during oven or stove use.	Chemiluminescent Analyzer

oven for cooking. Figure 3 presents the cumulative distribution of 2-hour daily peak NO_2 levels in the kitchens (1 meter from the stove) of two gas stove homes monitored in the Wade et al. study.[69,70] For example, approximately 95 percent of the daily peak 2 hour averages in the kitchens of the two homes were below 0.21 and 0.35 ppm, respectively.

The Wade et al. study[69,70] also demonstrated the differences that occur in levels of NO_2 for kitchens, living rooms, and bedrooms of gas stove homes. As one moved away from the source of NO_2, the kitchen stove and oven, NO_2 levels dropped off fairly rapidly. Short-term peaks in the bedrooms of Homes 1 and 3 were not significantly greater than outdoor peak levels. The 24-hour average concentrations were higher in the kitchens (means 0.04-0.06 ppm) than levels in other rooms of these homes or outdoors. However, the 24-hour concentrations were only slightly higher in the living room and bedroom of these homes (means 0.03-0.04 ppm) than the 24-hour levels observed outdoors (0.02 ppm).

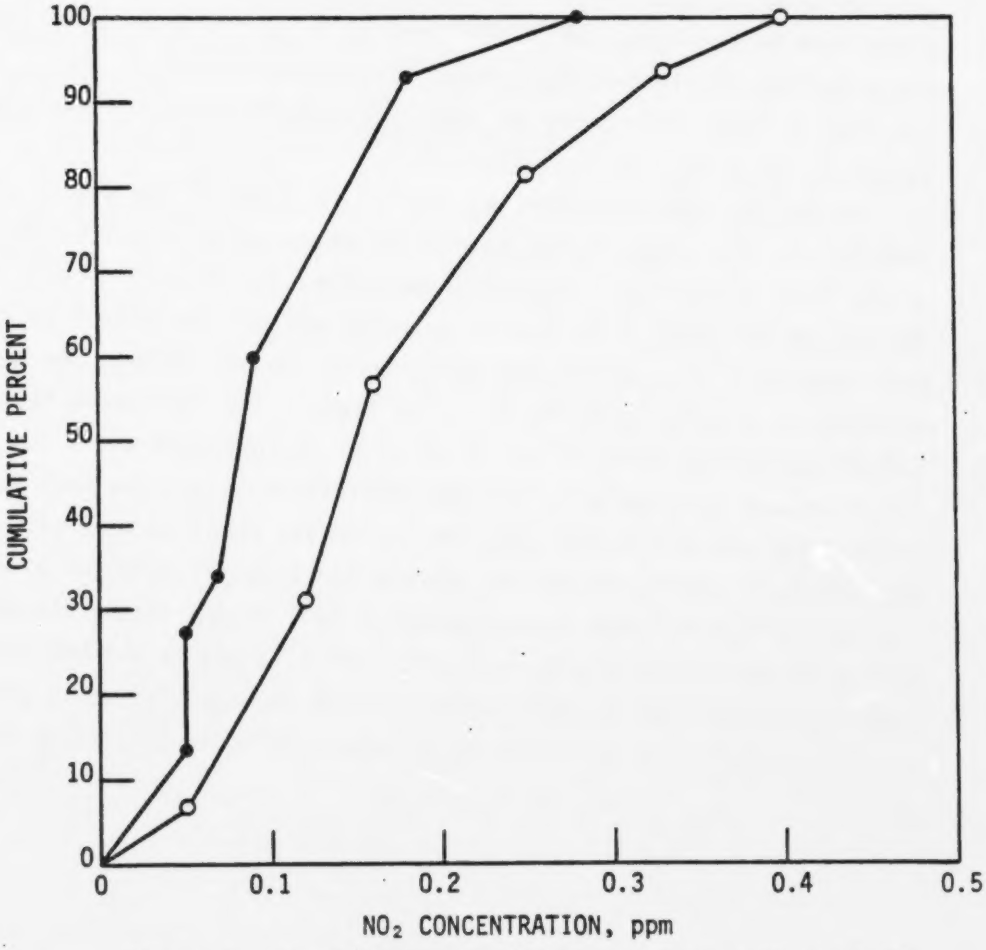


Figure 3. Cumulative distribution of 2-hr daily peak NO_2 concentrations in kitchens of two houses with gas stoves.

A number of studies[71-73] by the Lawrence Berkeley Laboratory have examined the contribution of gas stoves and ovens to NO_2 levels in energy efficient homes and test kitchens. Hollowel et al. (1980)[71] simulated typical gas stove use patterns, provided by the American Gas Association, in an energy efficient research house and monitored NO_2 levels in the kitchen, living room, bedroom, and outdoors. The peak hourly average observed during a 24-hour period and the 24-hour average for each of the monitoring locations are presented in Table 5. The levels were somewhat higher than would be expected in "average" homes due to the low air exchange rates. Older houses and most new houses have air exchange (ventilation and infiltration) rates of 0.8 - 1.5 air changes per hour (ach) or higher.[72,73] It has been estimated that well-constructed new single-family houses have air exchange rates in the range of 0.5-1.0 ach.[72] In contrast, new houses with energy conservation measures can limit air exchange rates to 0.2-0.5 ach.[72]

Hollowel et al. (1978)[72] monitored NO_2 levels in a test kitchen with a gas oven on for 1 hour at 350°F. Hourly concentrations of NO_2 were reported for a variety of air exchange rates. Increasing the air exchange rate resulted in lower NO_2 hourly average levels during use of a gas oven (see values in Table 5).

In another Lawrence Berkeley Laboratory study,[73] the effect of various ventilation strategies on NO_2 levels was examined in a test house during a simulated dinner meal. Figure 4 summarizes the results from this study. The values in Figure 4 for the range hood indicate the effect of adding spot ventilation in the kitchen and probably do not reflect the conditions existing in most homes in the Six-City Study. The difference between indoor and outdoor temperature is noted by ΔT in Figure 4. A low ΔT and low windspeed contribute to reduced ventilation rate. The peak hourly average NO_2 concentrations observed for an air exchange rate of 0.8-0.9 ach (which is approximately the average air exchange rate for existing residential houses) were approximately 0.18-0.30 ppm in the kitchen, 0.13-0.18 ppm in the living room, and 0.09-0.13 ppm in the bedroom. These peak hourly averages compare favorably with the range of daily peak 2-hour averages observed in the 3 gas stove homes monitored by Cote et al. (1974).[70]

NO_2 CONCENTRATION VS. VENTILATION

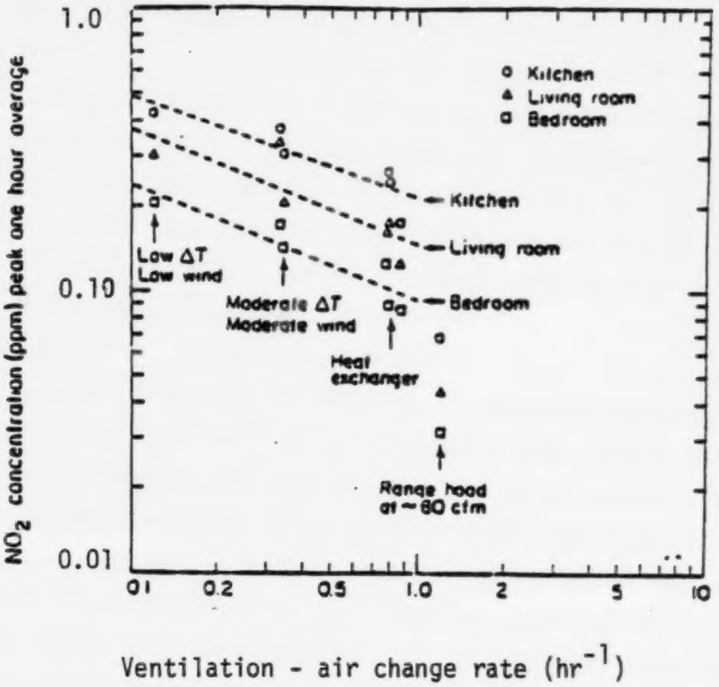


Figure 4. NO_2 concentration vs ventilation.

Even after estimating the concentrations of NO_2 which might be present in the gas stove homes, it is still difficult to determine the exposure to which children living in these homes may have been subjected. Because NO_2 levels differ substantially from room to room, activity patterns could substantially influence actual exposure. For example, a person who spent considerable time in the kitchen would probably be exposed more frequently to higher concentrations than a person who spent most of the day in other parts of the home.

Using the data from Cote et al.,[70] it is estimated that peak 2-hour concentrations ranged from 0.06 to 0.41 ppm across the various rooms and houses used in the study (see Table 5). In the Lawrence Berkeley Laboratory study,[73] peak 1-hour concentrations ranged from 0.13 to 0.30 ppm depending upon the room in the house. Since it is unknown what percentage of the time the children may have spent in the various rooms, it is necessary to use a range to estimate the exposure which may have been associated with the reported health effects. Using the above data, it would appear that a reasonable estimate of the 1-hour exposures to which the children may have been exposed more than a few times would lie in the range 0.15 to 0.30 ppm.

c. Staff Comments on Gas Stove Studies. In evaluating the evidence from the Melia et al. and Speizer et al. studies, the major uncertainties are what agent(s) caused the reported health effects and, if NO_2, then what exposure levels and patterns (concentration, averaging time, and frequency) are associated with the reported effects. Possible confounding and covarying factors which may be related to the increased prevalence rate of respiratory illness and symptoms observed in children in gas stove homes include humidity, socio-economic status, and pollutants other than NO_2, such as carbon monoxide and hydrogen cyanide, which are emitted when gas combustion occurs. However, there is no evidence that carbon monoxide or hydrogen cyanide are given off in dangerous quantities by gas stove combustion, and there is also no evidence that these pollutants cause effects such as increased respiratory symptoms or illness. The contribution, if any, to increased respiratory symptoms or illness due to increased humidity or water vapor in gas stove homes requires further research.

Other factors, such as outdoor pollution levels and exposure to parental smoking, may have contributed to the overall effect observed in the Melia et al. and Speizer et al. studies. There is, however, no evidence in the studies by Melia et al. and Speizer et al. to suggest that these factors differ for children living in electric versus gas stove homes.

The cumulative findings from a number of animal and human clinical studies also suggest that NO_2 is the principal agent responsible for the effects reported in the gas stove studies. As discussed in the earlier section on animal studies (V-C-1), controlled exposure studies of a variety of animal species have provided sufficient data to demonstrate that NO_2 impairs respiratory defense mechanisms, providing a plausible basis for inferring that NO_2 may have been associated with the reported increased incidence of acute respiratory illness in children living in homes with gas stoves. Controlled human exposure studies indicating increased symptomatic effects in asthmatics after exposure to 0.5 ppm NO_2 for 2 hours[32] and impaired pulmonary function after brief (3-10 minute) exposures to NO_2 concentrations in the range 1.0-2.0 ppm[31,36] also support the hypothesis that NO_2 is the principal agent causing the increased respiratory system effects observed in the gas stove homes.

Experimental work in developing an animal infectivity model also provides some evidence that NO_2 may be the agent causing the effects observed in the gas stove studies. The animal infectivity model studies have examined the influence of exposure mode (concentrations and time of exposure) on the toxicity of NO_2 (Gardner et al., 1977;[11] Coffin et al., 1977;[12] Gardner et al., 1979[13]). With concentration times time of exposure (CxT) held constant at 7 and varying concentration (1-14 ppm) and time (0.5-7 hrs.), Gardner et al. (1977)[11] demonstrated that brief exposures to high concentrations of NO_2 resulted in more severe infections and greater mortality than did prolonged exposures to lower concentrations. The findings of this study suggest that short-term peak exposures may be a more important factor than long-term, low-level exposures of equivalent dose in causing or contributing to the effect observed in gas stove homes.

In another animal study, Gardner et al. (1979)[13] examined the effect of background NO_2 concentrations on mortality in mice given a bacterial challenge 18 hours after a single peak exposure to NO_2. The mice were first exposed either to 1.5 ppm NO_2 or to no NO_2 for 64 hours. Then they were exposed to a single peak of 4.5 ppm NO_2 (for 1, 3.5, or 7 hours), followed by bacterial challenge 18 hours after exposure to the 4.5 ppm peak level. There was a statistically significant increase in mortality for the 3.5-hour and 7-hour exposure to 4.5 ppm NO_2 with a 64-hour pre-exposure background (1.5 ppm NO_2) over that observed with no pre-exposure background. The implications of this finding are that background concentrations (1) may affect the ability of animals to recover or adapt to the impact of peak exposures and/or (2) may impair the functioning of the lung's defense mechanisms (e.g., alveolar macrophages, leukocytes, and mucociliary system).

The same study[13] also examined the impact of multiple spikes (4.5 ppm) with a continuous background (1.5 ppm), compared to a continuous exposure (1.5 ppm) without spikes, on mortality of mice challenged with bacteria. The mice exposed to multiple spikes received a 1-hour exposure to 4.5 ppm NO_2 twice a day over a two week period. At the end of the two weeks, there was no statistically significant difference in mortality for the mice exposed to 1.5 ppm along with multiple spikes (4.5 ppm). The results of this study indicate the complexity of the relationship between exposure patterns and health effects and suggest that further research is needed to clarify the impact on increased susceptibility to infection of repeated peak NO_2 exposures with and without background NO_2 levels.

It also should be noted that, while the animal studies provide some evidence that NO_2 impairs respiratory defense mechanisms, this evidence comes from studies conducted at NO_2 exposure levels believed to be considerably higher than those experienced in the gas stove homes.

The authors of the Speizer et al. study[64] have hypothesized that repeated peak values are probably the most important exposures in causing the effects observed in the gas stove homes. Their judgment is in part based on the fact that there are no intermittent short-term (1/2 hour-2 hour) NO_2 peak concentrations in electric stove homes and that long-term (24-hour or longer) concentrations in gas stove homes are not that much higher than in electric stove homes.

The daily peak 2-hour NO_2 levels observed in 3 homes monitored by Cote et al. (1974)[70] provide the best, although rough, estimate of the short-term (1-2 hour) levels that may have occurred in the gas stove homes in the Speizer et al. (1980) study.[64] It is recognized that short-term levels in particular homes in the Six-City Study may have varied considerably in magnitude or frequency of peak levels from the homes in the Cote et al. (1974) study[70] due to variation in gas stove usage, ventilation conditions, and designs of homes.

D. Sensitive Population Groups

Based upon the health effects information provided in the Criteria Document and reviewed here, the groups that appear to be most sensitive to exposures to NO_2 include children, chronic bronchitics, asthmatics, and individuals with emphysema. Other individuals with impaired and/or sensitive respiratory or nasopharyngeal systems (e.g., individuals with symptoms of hay fever) may also be more sensitive to NO_2. In addition, there is reason to believe that persons with cirrhosis of the liver or other liver, hormonal, and blood disorders, or undergoing certain types of drug therapies may also be more sensitive to NO_2 because of the implications from animal studies showing increased systemic, hematological, and hormonal alterations after exposure to NO_2.

Health effects data from epidemiological studies in gas stove homes suggest that young children are at increased risk of respiratory symptoms and infection from exposures to elevated[64,57,58] concentrations of NO_2. This increased risk of respiratory symptoms may be due to either the higher activity level of children (i.e., increased dose) or the inherently greater biological sensitivity of children or both.

Sensitive groups such as children and asthmatics apparently respond most readily to acute exposures of NO_2. However, these groups and others may be subject to effects produced by long-term exposures that have not been adequately addressed in human studies. These include direct or indirect effects on lung tissue producing or aggravating emphysema, cardiopulmonary disease, and pneumoconeosis. Available information does not suggest major risks of such effects at current ambient levels in most U. S. areas.

Other groups at risk to NO_2 exposures are asthmatics and bronchitics. Human clinical study data[32] have provided evidence that some of these individuals suffer mild symptomatic effects (nasal discharge, headaches, dizziness, and labored breathing) after light to moderate exercise during an exposure to 0.5 ppm NO_2 for two hours. Chronic bronchitics showed increased airway resistance following approximately three-minute exposures at or above 1.6 ppm NO_2.[36] A more controversial study suggested that asthmatics experience an increased sensitivity to a bronchoconstricting agent following a one-hour exposure to 0.1 ppm NO_2.[38] However, a similar study (not yet published) conducted at the U.S. EPA facilities in Chapel Hill, North Carolina failed to find any statistically significant changes. Although there are no human experimental studies of NO_2 involving individuals with emphysema, it seems reasonable to include such persons in the category of high risk individuals since they suffer from major impairment in breathing capacity even in the absence of NO_2.

In 1970, the U.S. Bureau of the Census estimated the total number of children under five years of age to be 17,163,000 and between five and 13 years of age to be 36,575,000.[74] Data from the U.S. National Health Survey for 1970 indicate that there were 6,526,000 chronic bronchitics, 6,031,000 asthmatics, and 1,313,000 emphysematics at the time of the Survey.[75] Although there is overlap on the order of about one million persons for these three categories, it could be reasonably estimated that over twelve million persons experienced these chronic respiratory conditions in the U.S. in 1970. Table 6 summarizes supporting evidence and population estimates for the above-mentioned sensitive groups.

On the basis of the available effects data, the staff is focusing on children and persons with asthma, chronic bronchitis, and emphysema as the most sensitive population groups. Other persons such as those who have had hay fever or those with liver, hematological, or hormonal disorders also may be affected at low levels of NO_2. Due to the lack of human experimental data for these latter groups, however, EPA staff intends to recommend to the Administrator that the potential effects on such persons should be considered only in determining the margin of safety for primary NO_2 standard(s).

TABLE 6

Summary of Potentially Sensitive Groups**

Sensitive Group	Supporting Evidence	References for Supporting Evidence	Population Estimates
Children	Children under age 2 exhibit increased prevalence of respiratory infection when living in homes with gas stoves. Children up to age 11 exhibited increased prevalence of respiratory infections when living in gas stove homes.	Speizer et al, 1980[55] Melia et al, 1979[57]	age 0-5 17.2 million* age 5-13 36.6 million*
Asthmatics	Asthmatics reacted to lower levels of NO_2 than normal subjects in controlled human exposure studies.	Kerr et al, 1979[32] Orehek et al, 1976[38]	6.0 million*
Chronic Bronchitics	Chronic bronchitics reacted to low levels of NO_2 in controlled human exposure studies.	Kerr et al, 1979[32] Von Nieding et al, 1971[36] Von Nieding et al, 1970[37]	6.5 million*
Emphysematics	Emphysematics have significantly impaired respiratory systems. Because studies have shown that NO_2 impairs respiration by increasing airway resistance, it is reasonable to assume that emphysematics may be sensitive to NO_2.	Von Nieding et al, 1971[36] Beil and Ulmer, 1976[35] Orehek et al, 1976[38]	1.3 million*
Persons with Tuberculosis, Pneumonia, Pleurisy, Hay Fever or Other Allergies	Studies have shown that NO_2 increases airway resistance. Persons who have or have had these conditions may be sufficiently impaired to be sensitive to low levels of NO_2.	Von Nieding et al, 1971[36] Beil and Ulmer, 1976[35] Orehek et al, 1976[38]	unknown
Persons with Liver, Blood or Hormonal Disorders	NO_2 induces changes in liver drug metabolism, lung hormone metabolism, and blood biochemistry.	Menzel, 1980[26] Miller et al, 1980[18] Posin et al., 1979[39]	unknown

*1970 U.S. Bureau of Census and 1970 U.S. National Health Survey

**All subgroups listed are not necessarily sensitive to NO_2 exposure at low levels.

VI. Factors to be Considered in Selecting Primary Standards

This section draws on the previous evaluation of scientific information and summarizes the principal factors bearing on selection of primary NO_2 standard levels and on designating appropriate averaging times and forms. Preliminary staff recommendations on alternative approaches for making those choices are also presented.

A. Averaging Times

A number of controlled human exposure studies[31-33,36-38] have reported respiratory system effects associated with NO_2 exposures ranging from 3 minutes to 2 1/2 hours. Evidence from animal studies indicates that a variety of serious effects on the respiratory and host defense systems are associated with NO_2 exposures ranging from hours to years. For example. exposure of mice to a relatively low NO_2 concentration (0.1 ppm) for six months with daily 2-hour peaks of 1.0 ppm resulted in emphysematous alterations.[29] In addition, other morphological changes in the lung and increases in susceptibility to bacterial and viral infection have been demonstrated in several animal species exposed to long-term NO_2 concentrations.

Evidence from community indoor ("gas stove") studies[57,58,64] suggests that the rate of respiratory illness and respiratory symptoms is increased in homes with elevated NO_2 levels due to use of gas stoves. As indicated in Section V-C-5-b, annual average, 24-hour average, and 1-2 hour average NO_2 concentrations are generally somewhat higher in homes with gas stoves compared to electric stove homes. The increase in NO_2 concentrations in gas stove homes over that observed in electric stove homes becomes more apparent as the averaging time gets shorter. The authors of the Speizer et al.[64] study have speculated that the observed effects might be largely due to repeated short-term peaks of an hour or less duration which occur when the gas stoves are used for cooking. While it is more likely that the repeated short-term peaks are mainly responsible for the observed effects, the possible contribution of low-level chronic exposures to NO_2 cannot be ruled out.

While it is very difficult at this time to derive quantitative exposure-effect relationships for humans, we believe the health effects evidence indicates a need to protect against both short- and long-term effects associated with NO_2 exposures. This protection could be provided with separate averaing time standards for each exposure duration of concern or by setting one standard that effectively protects against several averaging time/concentration level combinations. For example, EPA could set an annual average standard to limit the magnitude and frequency of short-term peaks that occur in the ambient air. Alternatively, EPA could set a 24-hour standard that required a specific percent of the 24-hour averages in a year to be below the standard level. Retaining an annual average standard, as opposed to setting a standard based on a shorter averaging time such as 24-hours, permits the continued use of current data processing and reporting requirements.

B. Form of the Standard

The current NO_2 annual primary NAAQS is based on the arithmetic mean of all valid daily averages in a calendar year. The arithmetic mean is more sensitive to repeated short-term peaks than the alternative, which is the geometric mean, and its use is consistent with other standards. Therefore, if a long-term standard is set, we recommend it be based on the arithmetic mean.

If the Administrator were to establish a short-term (e.g., hourly average) standard to provide adequate protection against repeated peak exposures, then the staff recommends that the standard be stated in a statistical rather than deterministic form. This could be accomplished by either:

(1) setting a standard where an allowable number of exceedances of the standard level would be expressed as an average or expected number per year, or

(2) setting a standard where a given percent of the daily maximum hourly values would be expected to be less than or equal to the standard level.

The emissions reductions to be achieved in the required control implementation program would be based on a statistical analysis of the monitoring data over a multi-year period (e.g., the preceeding 3-year period).

The statistical form of the standard offers a more stable target for control programs and is less sensitive to truly unusual meteorological conditions than a deterministic form. The general limitations of the deterministic form are discussed in another paper.[76] Recognition of these limitations has led EPA to promulgate or propose statistical forms for the ozone and carbon monoxide standards.[77,78]

C. Level of the Standard

Controlled human exposure studies, while providing accurate measurements of exposure levels and conditions, have been limited to examining effects on adults of single, short-term exposures to NO_2 or simple combinations of pollutants. In addition, these studies are limited to studying "reversible" effects and only a few studies have involved population groups suspected of being particularly susceptible to NO_2 exposures. A variety of animal studies indicate a range of effects due to chronic and acute exposures, but whether these effects occur in humans and at what exposure levels remain uncertain. Finally, community epidemiological studies, while representing real world conditions, are limited in that they can provide no more than associations between pollutant exposures and observed health effects. It follows that, although the scientific literature supports the conclusion that various levels and exposure patterns of NO_2 pose risks to human health, the data only can identify the limits of a range within which a standard should be set, and specific numeric standard levels, frequency of exceedance, and averaging times largely are a public health policy judgment.

Conclusions which can be reached from health effects evidence described in section V are key to the standards selection process. These conclusions are summarized below:

(1) While the animal toxicology literature does not provide human effect levels at this time, it does indicate a variety of effects from acute, chronic, and combined chronic and acute exposures to NO_2. Findings from animal studies (e.g., emphysematous alterations in the lung, other morphological changes in the lung, and increased susceptibility to infection) suggest that chronic exposures or chronic exposures with repeated peaks may lead to serious adverse health effects in humans. These effects may include development or aggravation of chronic respiratory diseases and increased incidence of acute respiratory infection or disease. Less severe and generally reversible effects (e.g., biochemical changes, interference with hormone metabolism, possible interference with liver metabolism) have been reported in animals exposed to single, acute levels of NO_2 less than 0.50 ppm. More severe effects, such as increased susceptibility to infection and morphological changes in the lung, appear to be related to multiple exposures to NO_2.

(2) Controlled human exposure evidence (Kerr et al., 1979)[32] indicates that mild symptomatic effects (e.g., headache, chest tightness, and nasal discharge) can occur in some asthmatics after a 2-hour exposure to 0.5 ppm NO_2. We conclude that these effects adversely impact personal comfort and well-being and that they may constitute adverse health effects for some individuals by interfering with their normal functioning.

The lowest level at which statistically significant pulmonary function changes have been shown in controlled human exposure studies is in the range of 1.0 to 2.0 ppm for short durations (3 to 10 minutes). The effects were observed in healthy adults and chronic bronchitics at these levels. Other controlled human exposure studies provide little support for additive or greater-than-additive effects being associated with exposure to NO_2 in the presence of other ambient pollutants.

(3) The Chattanooga and Japanese community epidemiological studies provide little, if any, quantitative evidence to relate effects to specific NO_2 concentrations. The findings of these studies are, however, not inconsistent with the hypothesis that NO_2 in a complex mix with other pollutants in the ambient air adversely affects lung function and/or respiratory illness in children.

(4) The British and Harvard Six-City "gas stove" studies[64,65] provide suggestive evidence that young children are at greater risk of developing acute respiratory disease or respiratory symptoms due to exposure to gas combustion products of which NO_2 is a significant component. The findings from animal studies demonstrating reduced resistance to infection due to NO_2 exposure support the hypothesis that NO_2 is the primary agent responsible for the effects observed in the "gas stove" studies. Controlled human exposure studies which indicate increased symptomatic effects in asthmatics after exposure to 0.5 ppm for 2 hours[32] and impaired pulmonary function after brief (3-10 minute) exposures to NO_2 concentrations in the range 1.0-2.0 ppm[31,36] also support the hypothesis that NO_2 is the principal agent causing the increased respiratory symptoms observed in gas stove homes.

Animal infectivity model studies (e.g., Gardner et al., 1977[11] and Coffin et al., 1977[12]) suggest that short-term peak exposures may be more important than long-term, low-level exposures of equivalent dose in contributing to the effect observed in gas stove homes. The authors of the Six-City Study have also indicated that repeated peak concentrations are probably the most important exposures in causing the effect observed in the gas stove homes. Their judgment is in part based on the observation that long-term (24-hour or longer) NO_2 concentrations in gas stove homes are not that much higher than in electric stove homes, while high intermittent short-term (e.g., 1/2 hour-2 hour) NO_2 peak concentrations are only observed in gas stove homes.

(5) Based on the health effects evidence reviewed in the criteria document and this paper, the groups which appear to be most sensitive to NO_2 exposures include asthmatics, chronic bronchitics, children, and individuals with emphysema and other chronic respiratory diseases.

(6) Selecting an ambient air quality standard with an adequate margin of safety requires that uncertainties in the health effects evidence be considered in arriving at the standard. While the lowest NO_2 concentration reliably linked to identifiable health effects due to single or repeated peak exposures appears to be in the range of 0.5 - 1.6 ppm NO_2 (based on symptomatic effects[32] and pulmonary function impairment[31,36]), a clear threshold for adverse health effects has not been established. Several factors make it difficult, if not impossible, to identify the minimum NO_2 level associated with adverse health effects.

For ethical reasons, clinical investigators have generally excluded from studies individuals who may be very sensitive to NO_2 exposures, such as children, elderly individuals, and people with severe pre-existing cardio-pulmonary diseases. In addition, human susceptibility to health effects varies considerably among individuals, and it is not certain that experimental evidence has accounted for the full range of susceptibility. Finally, there is no assurance that all adverse health effects related to low level NO_2 exposures have been identified.

Factors we believe should be considered in the margin of safety for NO_2 include: (a) potentially sensitive populations that have not been adequately tested, (b) concern for repeated peak exposures[31,36] and delayed effects, seen in animal studies but seldom a part of human clinical study protocols, (c) implications of the Orehek et al. (1976) study[38] in which a bronchoconstrictor was used, (d) possible synergistic or additive effects with other pollutants or environmental stresses[43], and (e) uncertain exposure levels and averaging times associated with effects reported in the "gas stove" studies.

D. Staff Conclusions and Recommendations

Mild symptomatic effects in asthmatics have been observed at 0.5 ppm for 2 hours (Kerr et al., 1979).[32] Potentially more serious pulmonary function impairment has been demonstrated in chronic bronchitics (Von Nieding et al., 1971)[36] at or above exposures of 1.6 ppm for 3 minutes. Another study (Suzuki and Ishikawa, 1965)[31] demonstrated pulmonary function impairment in healthy adults exposed to 0.7 to 2 ppm for 10 minutes, and a study by Beil and Ulmer (1976)[35] found pulmonary function impairment for healthy adults exposed to 2.5 ppm for 2 hours. We conclude from these studies that single exposures to NO_2 in excess of about 1.0 ppm for periods in excess of one hour (equivalent to about 2 ppm for 10 minutes based on the observed relationship of air quality distributions for different averaging times) should be avoided. Also, since the mild symptomatic effects observed in asthmatics may be indicators of more serious effects, it would be desirable to prevent frequent exposures to NO_2 concentration levels above 0.5 ppm. These NO_2 exposures generally are higher than concentrations of NO_2 normally encountered in the ambient air.

At exposure levels less than 0.5 ppm the scientific data for humans are sparse and the results are inconclusive. The only extensive studies which report health effects in humans for short-term exposure of NO_2 at concentration levels comparable to those observed in the ambient air (less than 0.5 ppm for 1-hour or more) are the gas stove studies. These studies are important not only because the exposure levels are low but because they are the only significant studies involving one of the most sensitive population groups, namely children. The Criteria Document warns that considerable caution should be used in drawing firm conclusions from the gas stove studies. However, the tentative conclusion is that the observed health effects can be attributed to NO_2.

Because children living in the gas stove homes were potentially exposed on many occasions to maximum short-term NO_2 concentrations below 0.5 ppm, and because biological damage has been reported in animals exposed repeatedly to short-term peaks of NO_2, we conclude that it would be desirable to prevent multiple exposure to short-term NO_2 levels below 0.5 ppm. The data do not provide a clear indication of what this precise level should be, but it would appear that infrequent exposures to 1-hour average NO_2 concentrations in the range of 0.15 to 0.30 ppm should present minimal health risks to children and other sensitive population groups.

No reliable scientific data exist which directly demonstrate effects in humans as the result of chronic or long-term (days to years) exposure to NO_2 at levels comparable to those found in the ambient air but there is an extensive data base which demonstrates that very serious biological effects have been caused in a variety of animals as the result of long-term exposure to NO_2 at concentration levels above the long-term levels found in the ambient air. The seriousness of these effects, the similarities of the biological systems between humans and animals, and the absence of animal studies showing that these effects do not occur at lower exposure levels suggest that there is a definite, although unquantifiable, risk to human health from long-term chronic exposure to NO_2.

The data contained in section IV and Appendix B of this report indicate that in many of the areas where monitoring is currently being conducted the 1-hour concentrations of NO_2 seldom exceed the 0.15 to 0.30 ppm range. In fact, a review of the existing monitoring data indicates that in areas which currently meet the present 0.053 ppm annual standard, 1-hour average levels greater than 0.30 ppm occur only two to three days per year and these events are rarely on consecutive days. In these same areas there could be 10 to 20 days with 1-hour levels in excess of 0.15 ppm and such levels have occurred on as many as four consecutive days (exceptions to this latter observation occur in several California cities where 1-hour levels have exceeded 0.15 ppm on more than 40 days in a year, including as many as six consecutive days, even though the annual standard was met).

There appear to be at least two approaches which would provide adequate public health protection. First, a 1-hour average NO_2 standard could be established at some level below 0.5 ppm. Such a standard would incorporate a frequency of exceedance rate which would be related to the concentration level selected. Both the concentration level and exceedance rate would largely be based on judgment since the data are insufficient to specify either with any degree of precision. For example, the Administrator might choose a maximum 1-hour standard in the range of 0.15 ppm to 0.30 ppm which would have to be met for a specified number of days in the calendar year. Establishing a new short-term standard would require both EPA and the states to implement a new regulatory program since there now is no short-term NO_2 standard.

An alternative to establishing a new short-term NO_2 standard is to retain an annual standard at a level which will provide the desired protection against potential short-term effects. This could be accomplished without major changes in the existing regulatory program. In using an annual standard to protect against effects caused by short-term concentrations effects, it should be recognized that available human data on effects from long-term exposures are not sufficient to support a specific numerical standard.

The existing monitoring data can be used to help determine the appropriate level of an annual standard which would achieve the desired health protection objectives. In Figure 5, the expected numbers of days when 1-hour concentrations exceed 0.15 ppm and 0.30 ppm are plotted as functions of the annual average concentrations. The curves shown on the figure are based on data from a number of urban area monitoring sites. The upper portion of each curve is based primarily on California data and may overstate the situation in other cities.

From Figure 5, an annual standard of 0.05 ppm would be expected to prevent 1-hour NO_2 levels from exceeding 0.15 ppm levels on all but about 20 days per year, and from exceeding 0.30 ppm on all but two days per year. Thus, an annual standard of 0.05 ppm could be considered as a conservative surrogate to a short-term standard, and would tend to keep most 1-hour levels below 0.15 ppm.

The data in Figure 5 indicate that with an annual standard as high as 0.08 ppm, we would expect 1-hour NO_2 levels not to exceed 0.30 ppm on more than about 10 days per year, and essentially never to exceed 0.50 ppm.

A possible exception to the above analysis may be in areas in the immediate vicinity of large low-level point sources. While modeling results indicate that 1-hour NO_2 peaks above 0.5 ppm are theoretically possible around major NO_x point sources with low stack heights, the available monitoring data indicate 1-hour peaks of 0.30 ppm are rarely seen and hourly peak levels never have been reported at or above 0.50 ppm.

An annual standard in the range of 0.05 to 0.08 ppm would appear to provide adequate protection against the potential and uncertain health effects that may be associated with exposure to short-term NO_2 levels. Such a standard could be used as a surrogate for a short-term standard. In addition, an annual standard would provide some, although unquantifiable, protection against possible adverse health effects from long-term exposure.

The lack of scientifically demonstrated health effects in humans from NO_2 exposure in concentrations below 0.5 ppm could be interpreted to mean that there is no need for an NO_2 NAAQS. However, such an interpretation, we believe, would ignore the cumulative evidence from controlled animal and human exposure studies and community indoor studies which strongly suggest that NO_2 may cause adverse health effects in sensitive population groups exposed to NO_2 levels at or near existing ambient levels.

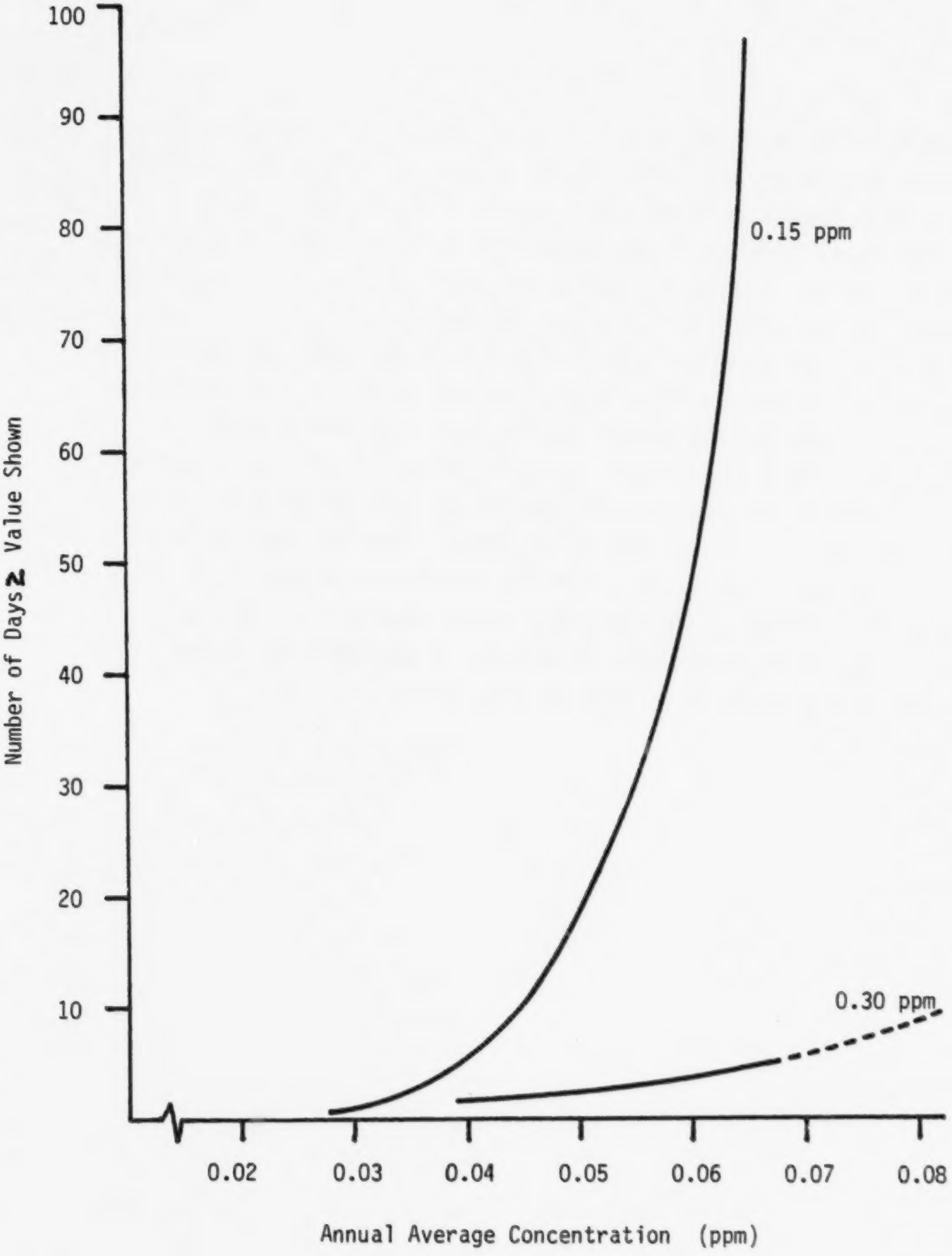


Figure 5. Expected Number of Days on Which Maximum 1-Hour NO2 Concentrations Exceed 0.15 and 0.30 ppm Associated with Annual Average Concentrations (based on SAROAD data for 14 sites during 1979-1980)

VII. CRITICAL ELEMENTS IN THE REVIEW OF THE SECONDARY STANDARDS

This section describes the welfare effects attributed to NO_2 and, where possible, sets forth judgments as to which levels of effects may be defined as adverse for standard setting purposes. The major categories to be addressed with regard to secondary standards are symptomatic effects, vegetation effects, visibility impairment and materials damage.

A. Personal Comfort and Well-Being

A secondary ambient air quality standard for a pollutant must specify a level of air quality that is adequate to protect public welfare from any known or anticipated adverse effects associated with the presence of the pollutant. As defined in section 302(h) of the Act, welfare effects include effects on personal comfort and well-being. Thus, in instances where observed effects are not clearly adverse to health but do affect personal comfort and well-being, the Act makes provisions for protecting against these effects through the secondary standard mechanism.

Effects which may well fall in this category are the mild symptomatic effects which were observed in 1 of 7 bronchitics and in 7 of 13 asthmatics during or after exposure to 0.5 ppm NO_2 for 2 hours in the Kerr et al. (1979) study.[32] The authors indicate that the symptoms were mild and reversible and included slight headache, nasal discharge, dizziness, chest tightness, and labored breathing during exercise. Although there is general agreement that these mild symptomatic effects are identifiable health effects, there is uncertainty as to whether they are adverse health effects and as such warrant protection under the primary standard. It does seem clear, however, that these symptomatic effects could cause personal discomfort and should be considered in setting either the primary or the secondary standard.

B. Vegetation Effects

1. Nature Of Effects

The most notable feature of the response of vegetation to NO_2 stress is the varied degrees of NO_2-induced injury. These differing responses can be explained in part by the physiological processes affecting NO_2 uptake into the leaf, pollutant toxicity at target sites, and cellular repair capacity. This section focuses on three major categories of effects: foliar injury, growth and yield reduction, and physiological and biochemical changes.

In regard to foliar injury, there is no "typical" leaf symptom or set of symptoms that reliably indicates plant exposure to NO_2. Acute and chronic exposures may produce different types of foliar injury including leaf chlorosis and necrosis. Data concerning the effects of NO_2 on plant growth and yield are limited. However, it is reasonable to assume that NO_2-induced reductions in assimilatory capacity of plants through altered metabolism or leaf injury may also affect the growth of plants.[79] Reductions in growth and yield are not always accompanied by foliar injury. Finally, pollutant reactions with cellular constituents can lead to physiological and biochemical changes such as altered metabolism, reduced photosynthesis, and probably many other effects which have been suspected but not yet observed or measured. These known and suspected effects may, in turn, lead to more profound effects at progressively higher levels of biological organizations (e.g., cellular organization, leaf injury, growth, yield).

The extent, severity, and type of NO_2 effects on plants can be altered by both external and internal factors. Environmental conditions, as well as the condition or status of the plant itself, influence the response of the plant to NO_2. Susceptibility of plants to NO_2 varies greatly among plant species and even among varieties, cultivars or clones of the same species. This varying susceptibility is due to genetic factors. Another important biological factor affecting the severity of damage is the stage of development or age of the plant or plant part. Studies have shown that the stage of development at which plants are exposed to NO_2 affects the degree of yield reduction.[79] For example, fumigation of oats during flowering has the greatest effects on the yield of grain. Exposures during the earlier, vegetative stage of development, or later when the grain is yellow-ripe, may have no effect on yield. The age of leaves also can affect their susceptibility to NO_2. Among the important environmental factors affecting plant sensitivity to NO_2 are the presence or absence of other pollutants, soil moisture, temperature, humidity, light intensity, and time of day at which exposure occurs.

a. Foliar Injury. The diagnosis of injury resulting from NO_2 is often difficult. The injury pattern may vary depending on species, cultivar, age of leaf, season of year, pollutant dose and prevailing environmental conditions. Acute exposures usually elicit completely different responses than chronic exposures. In acute exposures leaf injury is usually characterized by leaf necrosis. This is expressed as light brown irregularly shaped necrotic lesions, usually at or near the tips of leaves. The area affected varies with the magnitude of the exposure. Leaf chlorosis is a striking characteristic of the injury that occurs from long exposures to low NO_2 concentrations. This type of injury is expressed as greenish yellow spots or as yellowing of the entire leaf surface. Chlorosis may be limited to the leaf margin or may spread across the leaf surface.

b. Growth and Yield. Experimental data documenting the effects of NO_2 on plant growth and yield are limited.[79] As previously stated, it is reasonable to assume that NO_2-induced disruptions in plant function, such as changes in photosynthetic rate and leaf injury, affect the growth of plants. Foliar injury is an imprecise measure of the effect of NO_2 on growth and yield parameters. Growth and yield reductions can occur with minimal or no foliar injury and it is possible to have extensive foliar injury with no significant effect on crop yield.

c. Physiological and Biochemical Changes. Detection of injury from pollutants often requires the measurement of subtle responses such as photosynthesis, transpiration, and rates of metabolic processes. Effects at the cellular level have been related to effects on leaves and unusual physiological changes in the entire plant. Generally investigations have relied on visible leaf damage or symptoms of injury such as leaf lesions, color changes, or reductions in growth and yield as measures of effects. Although leaf injury is the most obvious effect of NO_2 on plants, it is only the end result of a series of events which have occurred at a sub-cellular level of biologic organization. Physiological changes such as reduction in photosynthetic rate occur in some species after being exposed to low levels of NO_2 before there is any visible injury. The interaction between genetics and environmental factors determines the sensitivity of plants to NO_2. The relative sensitivity of species or cultivars within a species can change, depending on the environmental conditions that exist. Other variables affecting plant response and ability to recover from NO_2-induced stress include the stage of development of the plant and the frequency and magnitude with which such stress occurs.

2. Effects From Exposures To NO_2 Alone

Evidence in the Criteria Document[80] as well as consultations with plant physiologists[81-83] have indicated that visible injury to vegetation from NO_2 alone occurs at levels which are above ambient concentrations generally occurring within the U.S., except around a few point sources. Several studies[84-88] on the effects of NO_2 alone on vegetation have failed to show plant injury at concentrations below 2 ppm for a short-term exposure. The lowest level of NO_2 alone that caused foliar injury has been estimated at 2 ppm for a four hour exposure.[80-81] The "time concentration model to predict acute foliar injury" developed by Heck and Tingey (1979) did not predict foliar injury at levels below 2 ppm for any crops tested.[89]

For long term exposures, such as a growing season, the lowest concentrations reported to depress growth are approximately 0.25 ppm.[83] Very few long-term studies have been conducted at concentrations below 0.25 ppm (Table 7). The concentrations reported in these studies are probably higher than those which would be expected to occur in the atmosphere for extended periods of time. The one exception is Ashenden et al., 1980[90] who reported that 0.11 ppm NO_2 (continuous exposure for 103.5 hours per week for 20 weeks) significantly reduced the growth of Kentucky bluegrass and affected some growth parameters of orchard grass. The exposure of these grasses occurred during the fall and winter when growth was slow. The author suggested that this might have made the grasses more susceptible to injury by pollutants and cites experiments which indicate that nitrogen oxides are more toxic to plants when growth is slow (Ashenden et al., 1980).[90]

TABLE 7

TABULAR SUMMARY OF EFFECTS OF NITROGEN DIOXIDE ON VEGETATION

Exposure Duration (Continuous)	Concentration (ppm)	Plant Species	Plant Response	Reference
90 min.	0.66	oat (*Avena sativa* var. Park) alfalfa (*Medicago sativa* var. Ranger)	Inhibition of rate of net photosynthesis	Hill and Bennett, 1970[92]
20 hrs.	0.25	tomato (*Lycopersicon esculentum* var. *Moneymaker*)	Inhibition of rate of net photosynthesis	Capron and Mansfield, 1976[91]
10-22 days	0.15-0.26	tomato (*Lycopersicon esculentum*)	Decrease in dry weight and leaf area; darker green color and downward curvacure of leaves	Taylor and Eaton, 1966[100]
35 days	0.5	navel oranges (*Citrus sinensis* Osbeck)	Severe defoliation and leaf chlorosis	Thompson et al., 1970[80]
8.5 months	0.25	navel oranges (*Citrus sinensis* Osbeck)	Increased defoliation and reduced yield	Thompson et al., 1971[101]
128 days	0.25	tomato (*Lycopersicon esculentum* var. *Moneymaker*)	Decrease in fresh weight yield (22%) average fruit wt (12%), and the number of fruit (11%)	Spierings, 1971[102]
Exposed continuously for 5 days per week (103.5 hrs/wk for 20 wks)	0.11	Orchard grass (*Dactylis glomerata* var. *Aberystwyth S37*)	21% reduction in leaf area, 7% reduction in dry weight of green leaves	Ashenden, 1979, 1980[97,98]
Exposed continuously for 5 days per week (103.5 hrs/wk for 20 wks)	0.11	Kentucky bluegrass (*Poa pratensis* var. *Monopoly*)	17% reduction in leaf area, 29% reduction in dry weight of green leaves	Ashenden, 1979, 1980[97,98]
Exposed continuously for 5 days per week (103.5 hrs/wk for 20 wks)	0.11	Italian ryegrass (*Lolium multiflorum* var. *milamo*)	1% increase above the control in leaf area, 10% reduction in dry weight of green leaves	Ashenden, 1979, 1980[97,98]
Exposed continuously for 5 days per week (103.5 hrs/wk for 20 wks)	0.11	Timothy (*Phleum pratense* var. Eskimo)	30% increase above control in reduction in leaf area, 14% increase above control in reduction in dry weight of green leaves	Ashenden, 1979, 1980[97,98]

More subtle responses such as changes in photosynthesis have been reported by Capron and Mansfield (1976)[91] who found a reduction in photosynthetic rate of tomato plants exposed to 0.25 ppm NO_2 or higher concentrations over a 20-hour period. Hill and Bennett (1970)[92] reported that NO_2 inhibited apparent photosynthesis of oat and alfalfa at concentrations below those that caused foliar lesions. The threshold dose for this inhibition was 0.6 ppm NO_2 in 90-minute fumigations. Full recovery from NO_2-induced inhibition of more than 25% required more than 4 hours. However, complete recovery of the plants was noted consistently within 1 day following fumigation.

3. Effects From Combined Exposures

Studies on mixtures of NO_2 and SO_2 have shown that the injury threshold for NO_2 can be significantly decreased with the addition of SO_2 (Table 8). Concentrations at which observable injury has occurred were well within the range of ambient concentrations of NO_2 and SO_2 in some areas of the United States. Responses to pollutant mixtures appear to vary with concentration, ratio(s) of pollutant concentrations, sequence of exposure and other variables.

Tingey et al. (1971)[93] reported that a 4 hour exposure of several crops to levels up to 2 ppm NO_2 and 0.5 ppm SO_2 caused no injury when administered singly. Slight foliar injury was observed at 0.05 ppm NO_2 and 0.05 ppm SO_2 for a 4 hour exposure. A mixture of 0.10 ppm NO_2 and 0.10 ppm SO_2 for 4 hours caused significant foliar injury to the upper leaf surface of oats (27%), radish (27%), soybean (35%), tobacco (11%), and tomato (1%). However, at 0.15 or 0.25 ppm NO_2 along with 0.25 ppm SO_2 foliar injury decreased dramatically. It is unclear why the pollutants appear to be acting antagonistically at these higher concentrations. The relative decrease in damage that is associated with increasing concentrations may result from other biological protective mechanisms (for example, closing of stomata at higher concentrations) or from the inability of cells to withstand repeated injury. Other studies on combined exposures for SO_2/O_3 have also shown that the synergistic response was most pronounced near the threshold doses of the two gases and that, as concentrations increase beyond the threshold doses, response diminishes (McDowall and Cole, 1971; Tingey et al., 1973).[94-95] Further research is needed to fully understand this phenomenon.

TABLE 8

PLANT RESPONSE TO NITROGEN DIOXIDE AND SULFUR DIOXIDE MIXTURES

Exposure Duration	Concentration (ppm) NO_2/SO_2	Plant Response	Plant Species	Exposure Chamber[a]	Mixture Response[b]	References
1 hr.	0.5/0.5	0-5% foliar injury	radish (*Raphenus sativa* cv. Scarlet Clove)	CE	+	Bennett et al., 1975[103]
1 hr.	0.05/0.05	Significantly decreased net photosynthesis	pea (*Pisum sativum*)	CE	0	Bull and Mansfield, 1974[105]
2 hrs.	0.15/0.15	7% reduction in apparent photosynthesis. Some tissue death	alfalfa (*Medicago sativa* var. Ranger)	GH	+	White et al., 1974[99]
2 hrs.	0.25/0.25	9% reduction in apparent photosynthesis	alfalfa (*Medicago sativa* var.Ranger)	GH	+	White et al., 1974[99]
4 hrs.	0.10/0.10	0-10% foliar injury	tobacco (*Nicotiana tabacum* cv. Bel W_3)	GH	+	Heck, 1963[104]
4 hrs.	0.05/0.05	0-2% foliar injury in 6 species	pinto (*Phaseolus vulgaris* cv. Pinto) oats (*Avena sativa* cv. Clintland 64) radish (*Raphanus sativa* cv. Cherry Belle) soybean (*Glycine max.* cv. Hark) tobacco (*Nicotiana tabacum* cv. Bel W_3) tomato (*Lyscopersicon esculentum* cv. Roma VF)	GH	0	Tingey et al., 1971[93]
same	0.10/0.05	9% foliar injury in tobacco. 0-1% foliar injury in 5 species.	same	GH	+	same
same	0.25/0.05	16% foliar injury in tobacco; 13% foliar injury in radish. 0-2% foliar injury in 4 species.				
same	0.05/0.10	0% foliar injury in 6 species	same	GH	+	same
same	0.10/0.10	1% foliar injury in tomato. 11-35% foliar injury in 5 species.	same	GH	+	
same	0.15/0.10	17-24% foliar injury in 6 species.	same	GH	+	same
same	0.05/0.20	6% foliar injury in soybean. 0-2% foliar injury in 4 species.	same	GH	+	same
same	0.20/0.20	0% foliar injury in tomato. 4-16% foliar injury in 5.				
same	0.05/0.25	7% foliar injury in soybean. 0-3% Foliar injury in 5 species.	same	GH	+	same
same	0.15/0.25	0-6% injury in 5 species.				
exposed continuously for 5 days a week. (103.5 hrs/wk for 20 wks)	0.11/0.11	72% reduction in leaf area. 83% reduction in dry weight of green leaves	Orchard grass (*Dactylis glomerata* var. Aberystwyth S37)	GH	+	Ashenden, 1979 1980[97,99]
same	0.11/0.11	84% reduction in leaf area. 83% reduction in dry weight of green leaves	Kentucky bluegrass (*Poa pratensis* var. Monopoly)	GH	+	same
same	0.11/0.11	43% reduction in leaf area. 65% reduction in dry weight of green leaves	Italian ryegrass (*Lolium multiflorum* var. Milamo)	GH	+	same
same	0.11/0.11	82% reduction in leaf area. 84% reduction in dry weight of green leaves	Timothy (*Phleum pratense* var. Eskimo)	GH	+	same

[a] CE, Controlled environment; GH, greenhouse.

[b] +, Greater than additive; 0, additive.

Ashenden (1978, 1979, 1980)[90,96-97] also reported growth and yield suppression from combined exposures of 0.11 ppm NO_2 and 0.11 ppm SO_2 (continuous exposure for 103.5 hours per week for 20 weeks). These exposures caused significant reductions in the growth parameters (5% significance or greater) of all four grass species tested. Many of the effects were judged to be synergistic.

Among the physiological changes reported for combined exposures was significantly decreased net photosynthesis in peas at 0.05 ppm NO_2 and 0.05 ppm SO_2 for 1 hour (Bull and Mansfield, 1974)[98]. White et al. (1974)[99] reported a 7% reduction in apparent photosynthesis and some tissue death after exposing alfalfa to a combination of 0.15 ppm NO_2 and 0.15 ppm SO_2 for 2 hours.

4. Staff Comments on Vegetation Effects

Because the Criteria Document cites a variety of effects of varying severity, a judgment must be made as to which effects are adverse. All identifiable plant responses, such as reductions in photosynthetic rates, leaf necrosis, yield reduction, etc., are not necessarily to be considered adverse.

In regard to NO_2, visible leaf injury is the most readily detectable and frequently reported symptom of exposure and for this reason has commonly been used in attempts to report damage to economic crops. Decreases in growth and yield can occur without such visible symptoms; however, since leaf injury is the most readily detectable and frequently reported symptom of NO_2 damage, this effect (foliar injury rates) is one possible basis the Administrator could use in setting a secondary standard. An alternative would be to make a judgment as to what other effect is to be considered adverse (e.g., slight foliar injury, growth and yield reduction) and set the standard at the level where this effect is determined to occur. Also of importance is the averaging time of any secondary standard established to protect vegetation. In our judgment, an averaging time of 1-3 hours would be most appropriate for effects on vegetation. This is because exposure to short-term peaks of NO_2 causes as much if not more damage to vegetation than does exposure over a growing season. In addition, by meeting a 1 to 3 hour standard at appropriate levels, there is a high probability of protecting against longer term effects based upon the relationship of short-term peaks to long-term means.

A key issue is whether there are enough data to quantify yield reduction at various ambient exposure levels. The Ashenden study[91] suggests that NO_2 alone may affect two grass species at relatively low ambient concentrations. The bulk of the data, however, suggests that the level at which NO_2 causes plant injury is well above the existing primary standard level (and presumably also above those primary standard levels likely to result from the current review of standards). In our judgment, there is inadequate evidence to demonstrate that exposure to NO_2 alone at low levels will lead to significant impacts on growth and yield for commercially important crops and indigenous vegetation. Based on our review of the literature and consultations with plant experts, we have formed a judgment that there are also insufficient data on the combined effects of NO_2 and SO_2 to do a quantitative evaluation of yield reduction for various ambient exposure levels. Numerous data points would be needed to run a model of this type effectively and they are not available. In addition, the limited data on combined exposure indicate that plant responses to NO_2 in the presence of other pollutants are extremely variable and are not fully understood at this point in time.

C. Visibility Impairment

1. Major Categories

Air pollution can degrade the appearance of distant objects and reduce the range at which they can be distinguished from the background. While visibility impairment can occur naturally, it is clear that anthropogenic air pollution in the form of fine suspended particles or NO_2 always exacerbates the problem. The effects are manifested both in visible plumes and in large-scale, hazy air masses over urban areas. For purposes of discussion, we are separating visibility impairment into two major categories: visible plumes or "plume blight" and urban scale "regional" haze. "Plume blight" may be defined as a coherent, identifiable plume, which can be seen as an optical entity against the background sky or a distant object. This definition assumes that a single source or a small group of sources produce pollutants that are not widely dispersed. Thus, plume blight is considered a near source or "local" problem. Absorption of light by NO_2 could cause the plume to appear brown in color. The prevalence of the visible brown plume phenomenon is not known with certainty. Brown plumes have been observed originating from a limited number of power plants in the Southwest.

The second category of impairment, regional haze, is produced from a multitude of sources and impairs visibility in every direction over a large area, such as an urban area, or possibly over several states. Objects on the horizon are masked and the contrast of nearby objects is reduced. In some cases, the haze may be elevated and appear as layers of discoloration. Multiple sources may combine over many days to produce haze, which may be regional in scale. The fate of haze is a function of meteorological processes that occur concurrently on larger scales of time and distance. For example, haze can result as a plume travels downwind and diffuses throughout the mixing layer, becoming less identified as a "plume," but more as a general haze, which obscures the view of distant objects.

2. Contributors to Visibility Reduction

Visibility impairment is caused by the scattering and absorption of light by particles and gases in the atmosphere and depends on the concentrations and properties of the gases present. Under typical ambient conditions, light scattering by particles dominates total extinction, which is related to reduction of contrast and visual range. The most significant optical effect of NO_2, however, involves discoloration.[106] NO_2 appears as a yellow to reddish-brown gas because it strongly absorbs blue light, allowing red wavelengths to reach the eye. The extent to which NO_2 filters out blue light is determined by the integral of NO_2 concentration along the sight path. The Criteria Document reports that less than 0.1 ppm-km NO_2 is sufficient to produce a color shift which is distinguishable in carefully controlled, color-matching tests. Reports from one laboratory using NO_2 containing sighting tubes indicate a possible visible color threshold of 0.06 ppm-km for the typical observer.[107] These values refer to the effect of NO_2 in the absence of atmospheric aerosol.

Although the physical properties of NO_2 are well known and its coloration effect in a controlled environment recognized, there are relatively little data available for judging the actual importance of NO_2 to visual air quality. The data needed to make such a judgment are potentially complex, including wavelength dependence of scattered light at different angles which can also cause discoloration (Charlson et al., 1978).[108] In addition to being modified by particle scattering, discoloration of plumes and haze layers by NO_2 also is affected by a number of other factors such as sun angle, surrounding scenery, viewing angle, human perception parameters, and pollutant concentrations.

One unresolved issue concerns the relative contribution of NO_2 and particles to atmospheric discoloration. Although the color of urban haze, often termed "brown," was originally ascribed to NO_2, more recently others have shown that brown color can result from particles alone (Charlson et al., 1978; Alquist and Charlson, 1969).[119,110] The coloration effect of particles depends on particle size, composition, the scattering angle between observer and illumination, and the optical characteristics of the background target. The overall impact of aerosol haze is to reduce visual range and contrast and possibly, to change color. A definitive assessment of the contribution made by nitrate aerosols to the degradation of visibility is not currently possible due to measurement problems, but the contribution of nitrate to fine particle mass is considered in the draft staff paper on particulate matter.

3. Staff Comments on Visibility

EPA must assess whether there is any supportable relationship between NO_2 concentrations at a given point and visibility impairment due to a plume or to regional haze. The present NO_2 standards are intended to protect against effects at or near ground level, and monitoring for NO_2 is generally performed at or near ground level. In the case of visual impairment due to a plume from a stationary source, there is no reliable relationship between ground, or near ground, level concentrations at any given point and discoloration caused by the plume. The plume, trapped in an atmospheric inversion, would disperse slowly and mix to the ground far downwind of the source. Concentrations taken at ground level while a coherent plume was clearly visible would not necessarily exceed an ambient standard. For this reason it would be difficult to set a NAAQS for NO_2, based on ground level monitoring, that would insure an acceptable level of visibility.

Another approach to establishing a visibility standard would be to monitor plume level concentrations. Because of the difficulty in making plume measurements, it may be possible to measure the discoloration itself using an optical device; e.g., a telephotometer. This instrument could measure the color contrast between the background and the plume. The measurements could be used as a possible index of the effect of NO_2. Measuring the actual discoloration would avoid the problems encountered in the ordinary approach, where a monitor near ground level might not pick up a violation of the standard, but a plume would be clearly visible, or where high NO_2 levels detected by remote sensing did not result in a perceptible plume. One problem in this approach is the uncertainty as to whether the discoloration that would trigger the telephotometer is caused by NO_2 or by particles. Although measurement of discoloration would be a unique way of expressing the standard, it would be worthy of consideration once these problems are resolved.

Another regulatory mechanism provided under sections 169A and 165(d) of the Clean Air Act (CAA) may provide some control over the more noticeable brown plumes appearing in otherwise pristine areas. On May 22, 1980, EPA proposed a phased approach to visibility protection (45 FR 34763). Phase I applies to pristine (class I) areas and requires control of visual impairment that can be traced to a single source or small group of sources, such as plumes emitted from tall stacks near class I areas. Mandatory class I Federal areas include all international parks and certain national parks and wilderness areas as described in section 162(a) of the CAA. EPA has initiated steps to control this aspect of visibility impairment because the modeling and monitoring techniques which address impairment caused by single sources will be available over the next few years, whereas similar techniques which deal with multiple source problems (regional haze) need additional research and will not be available for quite some time.

In regard to urban scale regional haze, because the effect of NO_2 depends on the product of the pollution concentration and the viewing path length, the impression of severity is greater the farther away the viewer can see past (or around) the haze layer. (The coloration of 0.05 ppm NO_2 over 10 km is the same as 0.5 ppm over 1 km.) When NO_2 is dispersed over a large area, as in the case of urban emissions, ground level concentrations at individual points may be less than a national standard but because an observer views the entire NO_2 mass, the urban plume would appear discolored.

In summary, the scientific evidence indicates that light scattering by particles is generally the primary cause of degraded visual air quality and that aerosol optical effects alone can impart a reddish brown color to a haze layer, thus raising the question as to the appropriateness of a NAAQS for NO_2 to protect against visibility impairment. While it is clear that particles and NO_2 contribute to brown haze, in our judgment the improvement in visual air quality to be gained by reducing NO_2 concentrations seems uncertain at best. Therefore, we conclude that an ambient standard for NO_2 to protect visibility is not warranted at this time.

D. Acidic Deposition

On August 20-21, 1980, the Clean Air Science Advisory Committee (CASAC) considered acidic deposition in connection with its review of a draft revised criteria document for particulate matter and sulfur oxides (PM/SO_x). The committee concluded that acidic deposition is a topic of extreme scientific complexity because of the difficulty in establishing firm quantitative relationships between emissions of relevant pollutants, formation of acidic wet and dry deposition products and the effects on terrestrial and aquatic ecosystems. Secondly, acidic deposition involves, as a minimum, the criteria pollutants of oxides of sulfur, oxides of nitrogen, and the fine particulate fraction of suspended particulates. Finally, the committee felt that any document on this subject should address both wet and dry deposition, since dry deposition is believed to account for at least one-half of the total acid deposition problem.

For these reasons, the committee felt that a significantly expanded and separate document should be prepared prior to any consideration of NAAQS as a regulatory mechanism for control of acidic deposition. CASAC suggested that a discussion of acidic precipitation be included in the criteria documents for both NO_x and PM/SO_x, but that plans be made for the development of a separate, more extensive document on acidic deposition. In response to these recommendations, EPA is in the process of developing an acidic deposition document that will provide a more comprehensive treatment of this subject. Thus, the issue will not be addressed in this staff paper.

E. Materials Damage

Field studies and laboratory research have demonstrated that nitrogen oxides can have deleterious effects on textile dyes, natural and synthetic fibers, metals, and various rubber products. Some individual dye fiber combinations exhibit color fading in response to NO_2 exposures. Significant fading was observed after 12 weeks of exposure to 0.05 NO_2 under high humidity and high temperature conditions. Studies conducted at levels of 0.2-0.3 ppm NO_2 for 8 to 16 hours have shown that NO_2 is the pollutant responsible for yellowing of various fabrics. Additional data are needed to define the role of nitrogen oxides in the degradation of textile fibers and rubber compounds and to define the effects of NO_2 on the corrosion of metals.

F. Staff Conclusions and Recommendations

The staff concludes that a primary standard within the recommended range will provide protection for the welfare effects discussed in section VII. Because acidic deposition is an important and complex problem associated with multi-pollutant interactions it is being addressed in a separate document by EPA and not as a specific element of the NO_2 standard review. The following conclusions are based on the assumption that a primary standard within the recommended range will be selected by the Administrator. If not, the need for a secondary standard must be reevaluated.

1. Symptomatic effects have been reported during or after exposure of asthmatics to 0.5 ppm NO_2 for 2 hours. The staff concludes that the occurrence of such symptoms affects personal comfort and well-being. Therefore, symptomatic effects may warrant protection under the secondary standard if they are not protected under the primary standard.
2. Effects of NO_2 alone on vegetation generally occur at concentrations above those which would exist in the atmosphere for any length of time. Although there is evidence that low levels of NO_2 and SO_2 combined can have a synergistic effect, this type of response is extremely variable and has not been sufficiently documented. Therefore the data do not suggest significant effects of NO_2 on vegetation below current ambient levels.
3. Although there is evidence that NO_2 contributes to atmospheric discoloration, the quantitative relationships between NO_2 concentrations and visibility impairment necessary for selecting the level of the standard have not been sufficiently established.
4. While NO_2 has been qualitatively associated with materials damage, the available data do not suggest major effects of NO_2 on materials for concentrations at or below the suggested ranges for the primary standard.

APPENDIX A. Review of Selected Animal Toxicology Studies

At the Clean Air Scientific Advisory Committee (CASAC) meeting held November 13-14, 1980,[4] three alternatives for use of animal data were considered. Generally, the options were: (1) to use the body of animal toxicology data qualitatively in developing a margin of safety; (3) to use the body of animal toxicology data quantitatively in developing a margin of safety; (3) to assess each type of biological effect (strength of data base, severity of effect, and relationship to human health effects) and then, as appropriate, to use the data base for each effect in either supporting a margin of safety or a lowest effects level in humans, or to consider the data base for a particular effect to be inadequate for use in setting NAAQS. The CASAC concluded that the third option was the best approach for analyzing animal data in the review of NAAQS for NO_2. In this revised version of the staff paper, we have attempted to refocus the discussion of the animal toxicology data in a manner that is consistent with the intent of option three.

While most animal studies involving NO_2 exposures have been conducted at relatively high concentrations of NO_2 (2 to 20 ppm), many studies conducted at lower concentrations (0.2 to 2.0 ppm) have shown that a variety of pulmonary and non-pulmonary effects do occur at lower levels. This section focuses primarily on those animal studies which have shown effects at lower levels ($\leq$ 2.0 ppm) of NO_2. When appropriate to show increasing degrees of toxicity, studies conducted at higher levels of NO_2 are included. The relevant toxicology studies are summarized in Tables 1 and 2. For a more complete review of NO_2 toxicology studies, the reader is referred to "Air Quality Criteria for Oxides of Nitrogen."[1]

A.1. Pulmonary Effects

Pulmonary effects resulting from exposure of experimental animals to NO_2 have been well-documented. These effects range from the relatively mild and reversible changes in pulmonary function following short-term single exposures to the more severe and permanent damage of emphysema for long-term continuous and repeated intermittent exposures to NO_2.

At concentrations near those which have been found in urban environments, the region of the lung bounded by the terminal and respiratory bronchioles and adjacent alveoli are most affected. This region

TABLE 1

Selected Animal Studies Demonstrating Effects for Short-Term Exposures to NO_2

NO_2 Concentration $\mu g/m^3$	ppm	Duration of Exposure	Biological Effect	Implications of Effect	References
380 3760 35,500	0.20 2.0 19.0	3 hours	Inhibition of prostaglandin E_2 breakdown after 18-hour delay (rat)	Significant time delay before appearance of effect; interference of NO_2 with hormone metabolism	Menzel, 1980[6]
380 to 94,000	0.20 to 50	4 hours	In vivo biosynthesis of nitrosomorpholine after pre-exposure to morpholine (mouse)	In vivo biosynthesis of carcinogenic compounds following exposure to NO_2	Iqbal et al., 1980[20]
470	0.25	3 hours	Increased pentobarbital-induced sleep time in females; effect disappeared for repeated exposures (mouse)	Suggests NO_2 interference with xenobiotic (liver) metabolism. Females more sensitive to a single NO_2 exposure; adaptation or tolerance; extrapulmonary effect	Miller et al., 1980[18]
470	0.25	4 hours/day, 5 days/week, 24 or 36 days	Isolated swollen collagen fibers (rabbits)	Repeated short-term exposures to NO_2 induce morphological alterations; extrapulmonary effect	Buell, 1970[17]
750	0.40	4 hours/day, 7 to 14 days	Proteinuria (proteinuim urine); an analysis revealed presence of albumin and α, β, σ globulins (guinea pig)	Repeated short-term exposures to NO_2 induce kidney damage	Sherwin and Layfield, 1974[16]
940	0.50	6, 18 or 24 hr/day, 12 months	Alveolar damage (mouse)	Repeated exposures to NO_2 induce morphological changes which reduce oxygen transfer capacity of lungs	Blair, et al., 1969[15]
750	0.40	4 hours/day, 7 days	Acid phosphatase levels increased (guinea pig)	Repeated short-term exposures to NO_2 alter enzyme levels in the lungs	Sherwin et al., 1974[19]
940	0.50	8 hours/day, 7 days	Increase in serum enzyme (LDH, CPK, SGOT, SGPT, CHE, lysozyme) levels in lungs; decrease in red blood cell glutathione peroxidase levels (guinea pig)	Repeated exposures to NO_2 alter enzyme levels in lungs, indicative of generalized damage to the lung	Donovan et al., 1976[25] Menzel et al., 1977[26]
940	0.50	Intermittent 6 to 18 hr/day, for 6 months followed by challenge to K. Pneumoniae	18% increased mortality ($p < 0.05$) over controls due to decreased resistance to infection (mouse)	Repeated exposures to NO_2 reduce resistance to bacterial infections	Ehrlich and Henry, 1968[14]

TABLE I (Continued)

Selected Animal Studies Demonstrating Effects for Short-Term Exposures

to NO_2

NO_2 Concentration $\mu g/m^3$	ppm	Duration of Exposure	Biological Effect	Implications of Effect	References
940 and 1880	0.50 and 1.0	4 hours and 1 hour	Degranulation of mast cells (rat)	Single NO_2 exposures cause release of substances with various activities including ability to increase airway resistance	Thomas et al., 1967[122]
1000	0.53	8 hours/day 180 days	Alterations in levels of variety of brain enzymes (guinea pigs)	Repeated NO_2 exposures may induce changes in brain enzyme levels; extrapulmonary effect	Drodz et al., 1975[129]
1880 3760 5600	1.0 3.0	3 hours followed by challenge with *S. pyogenes*	Increased mortality only for animals exposed to 3 ppm NO_2 during exercise (mouse)	Single exposure to NO_2 during exercise increase susceptibility to infection at or above 2.0 ppm	Gardner and Graham, 1976[21]
2800	1.5	Continuous or 7 hr/day 7 days/wk followed by challenge with *S. pyogenes*	After 1 week, mortality with continuous exposure greater ($p < 0.05$) than that for intermittent. After 2 weeks, no significant difference between continuous and intermittent exposure (mouse)	Even though total dose is greater for continuous exposure, susceptibility to infection becomes equivalent for continuous and intermittent over time, suggesting repeated peaks are more important than continuous levels of NO_2	Illing et al., 1980[131]
3760	2.0	3 hours followed by challenge with *S. pyogenes*	Increased mortality ($p < 0.05$) (mouse)	Single exposure to NO_2 can increase susceptibility to infection	Ehrlich et al., 1977[112]
6600	$\leq$ 3.5	$\leq$ 6 hours followed by challenge with *S. pyogenes*	Increased mortality by 31.9%. Concentration (ppm) x time (hr) = 21 (mouse)	For a given dose (CXT) concentration has a greater effect than time	Gardner et al., 1979[13]
6600	3.5	Continuous or 7 hours/day 7 days/week 15 days	Increased mortality with increased duration of exposure. No significant difference between continuous and intermittent exposure. With data adjusted for total difference in CxT mortality essentially the same (mouse)	Concentration is more important than duration of exposure in determining effects from a given dose	Gardner et al., 1979[13]

TABLE 2

Selected Animal Studies Demonstrating Effects for Long-Term Exposures to NO_2

NO_2 Concentration $\mu g/m^3$	ppm	Duration of Exposure	Biological Effect	Implications of Effect	References
188	0.1	Continuous for 6 months with 1.0 ppm spikes for 2 hr/day	Structural alterations in bronchioles and alveolar ducts (mouse)	Combination of very low level continuous exposure to NO_2 with daily peaks causes emphysema like changes in relatively short time period	Port et al., 1977[29]
680	0.36	Continuous for 7 days	Red blood cell D-2,3-diphosphoglycerate was significantly increased ($p < 0.05$) (guinea pig)	This may be indicative of tissue deoxygenation	Mersch et al., 1973[28]
750	0.40, 1.0	Continuous for 7 days	Increase in lung protein content (Vitamin C deficient guinea pig) in one study, but, another at the lowest concentration	Most likely due to plasma leakage which may be indicative of pulmonary edema and cell death; Vitamin C deficiency increases susceptibility	Sherwin and Carlson, 1973[117] Selgrade et al., 1981[24]
750 to 1880	0.4 to 1.0	Continuous for 17 to 18 months	Reduction in growth rate and body weight; growth improved by dietary Vitamin E supplement (mouse)	NO_2 impairs metabolism and growth process	Csallany, 1975 Csallany and Ayaz, 1978
940	0.5	5 days/week for 3 or 6 weeks	increased retention of protein in pulmonary air spaces (mouse)	Suggestive of pulmonary edema	Sherwin et al.,[121] 1977
940	0.5	Continuous for 14 days	Protein (Albumin and globulins) in urine (guinea pig)	Suggestive of kidney damage	Sherwin and Layfield, 1974[16]
940	0.5	Continuous for 7 days	Higher lysozyme, plasma cholinesterase, and other enzyme levels (guinea pig)	Indicative of liver and heart damage	Menzel et al., 1977[25] Donovan et al., 1976[26]
940	0.5	Continuous for 4 months	Alterations in blood enzyme levels (guinea pig)	Indicative of liver damage (hepatic lesions)	Menzel et al., 1977[25] Donovan et al., 1976[26]
940	0.5	Continuous for 90 days or 12 months followed by challenge of *K. pneumoniae*	Increased mortality ($p < 0.05$) after 90 days and after 12 months due to respiratory infection (mouse)	NO_2 increases susceptibility to respiratory infection	Ehrlich and Henry, 1968[14]
940 to 1880	0.5 to 1.0	Continuous for 39 days followed by challenge of A/PR/8 virus	Significantly increased rate of respiratory infection (female mouse)	NO_2 increases susceptibility to respiratory infection	Ito, 1971[133]

TABLE 2 (Continued)

Selected Animal Studies Demonstrating Effects for Long-Term Exposures to NO_2

NO_2 Concentration $\mu g/m^3$	ppm	Duration of Exposure	Biological Effect	Implications of Effect	References
940	0.5	Continuous exposure for 5 days/week (21, 28, 33 weeks) with daily 1-hour peaks of 2 ppm	Alveolar macrophage damage and morphological alterations (mouse)	NO_2 reduced effectiveness of pulmonary defenses	Aranyi et al., 1976[22]
940	0.5	Continuous for 12 months	Loss of cilia, alveolar edema, bronchial hyperplasia, fibrosis (mouse)	Various pulmonary effects indicative of potentially serious lung damage. Reduction in resistance to respiratory infection. Evidence suggestive of changes in terminal bronchioles; decreased clearance of particles	Hattori and Takemura, 1974[134] Hattori, 1973[135]
940 to 1500	0.5 to 0.8	Continuous for 1 month	Damage to tracheal mucosa and cilia (mouse)	Reduction in resistance to respiratory infection; decreased clearance of particles	Hattori et al., 1972[118] Nakajima et al., 1969[136]
1500	0.8	Continuous for 33 months	Decreased respiratory rate (∿ 20%). Gross and microscopic alterations (rats)	Evidence suggestive of microscopic changes in terminal bronchioles	Freeman et al., 1966[120]
1880	1.0	Continuous for 493 days, challenge 5 times with monkey adapted influenza virus	Reduced immunological activity; slight emphysema thickened bronchial and bronchiolar epithelium (monkey)	NO_2 reduces effectiveness of pulmonary defenses and may induce morphological changes	Fenters et al., 1966[116]
1880	1.0	6 months continuous, followed by intranasal challenge with D. pneumoniae	Increased respiratory infection and mortality (guinea pig)	NO_2 reduces ability to defend against pulmonary infection	Kosmider et al., 1973[23]
3760	2.0	Continuous for 43 days	No changes in terminal bronchi. Cilia lost and altered by 72 hours. Greater cilia loss and focal hyperplasia by 7 days. Regeneration of cilia by 14 days. Substantial recovery by 21 days (rat)	Suggestive of adaptation or tolerance to NO_2	Stephens et al., 1972[124]
3760	2.0	Continuous for 14 months	Hypertrophic epithelium, particularly in the area of respiratory bronchiole (monkey)	Advanced stage of morphological damage	Furriosi et al., 1973[137]

represents the terminal position of the lung which is primarily involved in oxygen and carbon dioxide exchange and is, therefore, one of the most essential regions of the lung for maintenance of life.[1]

a) Respiratory Infection. The pulmonary system normally defends itself against infection through a combination of mucociliary transport, phagocytosis, and immunological activities. These defenses, however, begin to break down during short-term and long-term exposures of animals to NO_2 with a resulting increase in susceptibility to respiratory infection.

Interpretation of studies such as that of Speizer et al (1980),[55] discussed in Section V-C-5, can be aided by supporting evidence from animal infectivity studies. Controlled exposure studies of a variety of animal species have provided sufficient data to demonstrate that NO_2 impairs respiratory defense mechanisms. The key animal studies are reviewed and summarized in this subsection.

One of the more extensive areas of investigation for NO_2 effects involves assessing the ability of this gas to enhance susceptibility to infectious agents. The infectivity model system involves first exposing randomly selected animals to either a test pollutant or to filtered air. Following exposure, both experimental (e.g., NO_2-exposed) and control animals are combined in another chamber where they are exposed for about 15 minutes to an aerosol containing one of several different infectious agents. The animals are then returned to clean air conditions for 15 days, and mortality rates of the experimental and control groups are compared. Mortality is normally due to pneumonia or related complications. Typically NO_2 increases this mortality.

The influence of exposure mode (concentration x time) on the toxicity of NO_2 has been investigated.[11,12,13] While holding concentration times time of exposure (C x T) constant at 7 and varying concentration (1 to 14 ppm) and time (0.5 to 7 hr), the authors reported that brief exposures to high concentrations of NO_2 resulted in greater mortality to bacterial infection than did prolonged exposures to lower concentrations of NO_2.[11] Thus, susceptibility to infection is influenced more by concentration of NO_2 than by length of exposure. Another study[13] evaluated the effect of varying continuous exposure durations on mice exposed to six different constant concentrations ranging from 0.5 to 28 ppm. The linear dose response curves observed in this investigation suggested that (1) mortality increases with increasing time of exposure, (2) mortality increases with increasing concentrations of NO_2, and (3) concentration is more important than time.

The importance of background NO_2 concentrations in increasing mortality was demonstrated in a study which reported greater effects for delayed bacterial challenge when mice received a 64 hour background exposure of 1.5 ppm NO_2, compared to zero background NO_2, with both exposure conditions superimposed on 1-hour peaks of 4.5 ppm NO_2.[21] This conclusion regarding long-term background exposures does not detract from the impact of exposure to short-term higher-level peaks for which several studies[11,111-113] have shown serious effects at or below 3.5 ppm. The above cited studies, in conjunction with the "gas-stove" studies,[55,57,58] provide evidence suggesting impairment of the respiratory defense mechanisms by NO_2.

The large number of investigators reporting significant effects using the infectivity model precludes thorough discussion of the individual studies. An overview of animal infectivity studies indicates that all of the infectivity studies which show effects below 2.0 ppm NO_2 are for long-term (continuous or intermittent) exposures, thus supporting the need for protection against long-term, low-level exposures to NO_2. Further discussion of specific aspects of impairment follows.

b) Respiratory Defense. The mucociliary system is a major line of defense against respiratory infection. This system extends from the nasal cavity down to the terminal bronchioles and removes particles of various types (inhaled particles, cellular debris, etc.) from the tracheobronchial tree. Concentrations of NO_2 greater than 5.0 ppm have been shown to cause decreased rates of ciliary beating *in vitro*[114] and of mucociliary transport *in vivo*.[115] These studies suggest that ciliary activity is reduced by exposure to NO_2. Other research has shown structural alterations in cilia and cilia-bearing cells.[118,126]

Alveolar macrophages are cells that phagocytize (consume) microbes and residual particles from the deeper portions of the lung. It has been demonstrated that 21-to 33-week continuous exposures of mice to concentrations as low as 0.5 ppm NO_2 with 1-hour peaks of 2.0 ppm NO_2 caused some morphological changes and complete deterioration of alveolar macrophage cells, while continuous exposure to 2.0 ppm NO_2 for 21 weeks caused distinct morphological alterations.[22] Reduced mobility and activity of alveolar macrophage cells decrease the pulmonary system's ability to defend itself against infection and may leave defense in non-ciliated regions of the lung entirely up to the immune system.

The immune system also has an essential role to inactivate bacteria and viruses. It functions in conjunction with other host defense systems and in their absence. Even though local immunological responses within the lung are critical for antimicrobial defense, the effects of pollutants on these responses are largely unstudied. Continuous exposure of monkeys to 1 ppm NO_2 for 493 days, followed by challenge with flu virus not only increased antibody levels in the blood prior to viral challenge but also increased the levels sevenfold and elevenfold, after 21 days and 41 days following viral challenge, respectively.[116] However, mice exposed for 3 months to a baseline of 0.5 ppm NO_2 with daily (5 days/week) 1-hour peaks of 2 ppm NO_2, exhibited a decrease in serum antibody levels. Immunoglobulin levels were also affected. In a different study[23] involving guinea pigs, it was claimed that NO_2 had an adverse effect on the immune function. This conclusion was drawn after a 6-month exposure to 1.0 ppm NO_2, followed by bacterial infection with Diplococcus pneumoniae, resulted in increased incidence of infection, reductions in all immunoglobulin fractions, and increased mortality.

The available data suggest serious effects from long-term low-level NO_2 exposure for the immune systems of several species. In combination with the evidence for mucociliary system and alveolar macrophage cell damage, these data support the contention that pulmonary defense mechanisms are adversely affected following acute and chronic exposures to NO_2. Thus, it is reasonable to suggest that NO_2 may be a factor of increased prevalence of respiratory illness for young children living in homes with gas stoves.

c) Lung Biochemistry. Lung biochemistry studies generally involve procedures which would be unethical for human subjects since the lungs are removed for detailed examination. Therefore, essentially all of our information on effects of NO_2 upon lung biochemistry is from a variety of animal species. However, human and animal biochemical reactions with NO_2 should qualitatively be quite similar due to the similarity of biochemical mechanisms.

While many lung biochemistry investigations have focused on mechanisms of toxicity (discussed in Section IV-B), those studies of primary concern in this discussion deal with detection of biochemical indicators of early damage from NO_2 exposure. There is of course a direct relationship between the mechanism of toxicity, which is primarily oxidative damage, and the resulting oxidative breakdown products which are involved in cell injury or death.

The lowest level of NO_2 for which biochemical effects have been demonstrated for a single exposure of 3 hours is 0.2 ppm.[19] In this study, 40 to 60% inhibition of conversion of prostaglandin E_2 (PGE_2) to its metabolite, 15-keto PGE_2, was produced in rats exposed to 0.2, 2.0, and 19 ppm NO_2, but the effect did not occur until 18 hours after exposure. The results of this particular study suggest the possibility of effects which may have been missed in human clinical studies due to the long delay between exposure and effect. In addition, this is the first documented case of NO_2 interference with hormone metabolism, and it shows an effect on a type of cell (endothelial cells of lung capillaries) not previously studied.

Continuous exposure of guinea pigs, theoretically deficient in Vitamin C, for one week to 0.4 ppm NO_2 increased lung protein content, possibly due to plasma leakage.[117] This was indicative of pulmonary edema but no differences in protein composition were reported. A more recent study by Selgrade et al. 1981[24] did not report alterations at the 0.4 ppm NO_2 exposure level; however, Vitamin C deficient guinea pigs were more susceptible to NO_2 as evidenced by increased protein in lung lavage fluid. The seriousness of changes in serum enzyme levels found in guinea pig lungs after repeated 8 hr/day for 1 week and long-term continuous exposures to 0.5 ppm NO_2 is uncertain;[25,26] some changes may be indicative of generalized damage to the lung.

These studies report that biochemical alterations are occurring after exposures to concentrations of NO_2 in the range of 0.2 to 0.5 ppm and support other investigations indicating a mechanism of membrane damage by chemical oxidation of unsaturated fatty acids. The delayed effect of NO_2 is important and may occur in humans, thus supporting a need for extended observation of human subjects following exposure. It is also possible that existing human studies reporting no biochemical alterations may have overlooked delayed effects.

d) Lung Morphology. Morphological alterations of lung tissue observed after long-term exposure to NO_2 are serious health effects because they may produce conditions such as emphysema, which are potentially irreversible and generally disrupt the lungs' ability to exchange oxygen. While those changes produced by short-term exposures to NO_2 appear to be generally reversible, the relationship of the acute effects to chronic effects is unclear at present.

Exposure of mice to 0.1 ppm NO_2 for six months with daily 2-hour peaks of 1.0 ppm NO_2 resulted in structural alterations in bronchioles and alveolar ducts.[29] While the emphysematous alterations were not remarkable in this study, the fact that the changes were found following extended exposure to very low concentrations of NO_2 is a matter of concern.

Several different effects have been reported for extended exposures between 0.5 and 1.0 ppm NO_2. These effects include: (1) isolated swollen collagen fibers (morphological damage) in rabbits exposed for 4 hours/day, 5 days/week for 24 or 36 days to 0.25 ppm NO_2;[17] (2) alveolar damage in mice after 6, 18 or 24 hour/day exposures for 12 months to 0.5 ppm NO_2[15]; (3) damage to tracheal mucosa and cilia in mice following 1 month of continuous exposure to 0.5-0.8 ppm NO_2[118]; (4) slight emphysema, thickened bronchial and bronchiolar epithelium in virus challenged monkeys caused by 493 days of continuous exposure to 1.0 ppm NO_2[119]; and (5) increased presence of protein in pulmonary air spaces, suggestive of edema, was found in mice following exposures to 0.5 ppm NO_2 for 5 days/week for 3 or 6 weeks.[121]

The process of emphysema development caused by NO_2 exposure is very complex, beginning with essentially mild reversible changes and leading eventually to irreversible changes and major damage for long-term exposures. Considering the life span of most experimental animals, it is reasonable to compare the time required for morphological damage in experimental animals with the time required for development of emphysema in humans. The seriousness of the effect, the large body of scientific evidence, and the comparability of effects found in humans support the need for protection of humans from long-term and multiple exposures to NO_2.

e) Pulmonary Function. Pulmonary function tests have been probably the most commonly used measures of pollutant effect for both epidemiological and controlled experimental human studies. Although pulmonary function measurements create less discomfort for subjects, are less invasive, and raise fewer ethical challenges than techniques used in most morphological or biochemical studies, pulmonary function tests measure only gross effects and provide less specific information, particularly for short-term low-level exposures to NO_2. There are no studies reporting serious pulmonary function changes in animals for short-term exposures below 5.0 ppm NO_2 and only a few studies reporting significant pulmonary function effects for long-term exposures below 5.0 ppm. However, it should be noted that more sophisticated tests for pulmonary function in small animals have been developed only recently.

Degranulation of mast cells was reported in rats sacrificed immediately after a 4-hour exposure to 0.5 ppm NO_2 or a 1-hour exposure to 1.0 ppm NO_2.[122] Although the effects reported for the short-term single exposure appeared to be reversible, the authors contended that release of granular material from the lung mast cells may suggest a potential onset of acute inflammatory reaction. Since the granular material (histamine and other chemicals) can cause bronchoconstriction, this effect may be related to increased airway resistance caused by NO_2 in humans.

One of the more common effects of exposure to NO_2 is tachypnea (increased respiratory rates). This effect was found for a variety of animal species exposed for both long-term continuous and short-term durations to NO_2 in the range of 0.5 to 20 ppm.[123] The large number of studies reporting this effect precludes discussion; however, it can be surmised that humans exposed to high NO_2 doses would also experience increased respiratory rate.

An overview of pulmonary function effects of short-term and long-term exposures of animals to 5.0 ppm NO_2 or less provides little support for the pulmonary function decrements found in humans. The only consistent effect found below 5.0 ppm was tachypnea, which was quickly reversible after removal of NO_2.

f) Adaptation. Adaptation and tolerance are terms commonly used to describe the ability of living systems to return to normal physiological conditions following extended biological stress. Adaptation is suggested as a possible explanation for results such as those found by Rejthar and Rejthar (1974),[124] which indicated that, after 7 weeks of exposure to 0.5 ppm NO_2, the lungs of exposed mice were in a state of repair and reversal of hyperplasia. Since longer-term studies have shown that the lungs have become emphysematous,[125-127] this reversibility after a shorter exposure should not cause complacency. For example, dogs exposed to a combination of 0.64 ppm NO_2 and 0.25 ppm NO exhibited progressive morphologic alterations after exposure ceased.[30]

A possible explanation for the apparent tolerance which many animal species exhibit has been offered.[1] At some point after initiating continuous NO_2 exposure, the rate of replacement of dead and injured cells may return to normal (i.e., rates of replacement equivalent to those in animals breathing clean air). Biochemistry (enzyme levels) of the adapted cells may have changed to permit degradation of secondary products formed during NO_2 inhalation. It has been speculated that levels of several protective enzymes in the rat may be either increased as a defense mechanism or may result from increased production of specific cells which produce more of these enzymes.

It is possible that all pulmonary cells are susceptible to low levels of NO_2 and that tolerance in the literal sense never really develops. Long-term low-level NO_2 exposure of animals and humans may create an insensitivity which may minimize pulmonary function response to NO_2 inhalation. A major pathophysiological change in pulmonary tissue may be necessary before pulmonary function is altered sufficiently to be detected by some pulmonary function test methods. Even though they are more sensitive, morphological and biochemical techniques cannot be used on humans due to ethical limitations.

Short-term peaks of NO_2 as well as long-term, low-level exposures to NO_2, appear to cause adverse health effects in spite of apparent adaptation to NO_2. The weight of scientific evidence supports some form of adaptation in several animal species, but there is also evidence to support the contention that these "adapted" animals are more likely to develop respiratory infections from short-term peak exposures[21] or emphysema from long-term exposures to NO_2.[118,30]

A.2. Extra Pulmonary Effects

Extrapulmonary effects are those biological alterations from normal physiological conditions which occur outside the pulmonary system. Extrapulmonary effects of NO_2 exposure include hematological (blood chemistry) effects, central nervous system and behavioral effects, and biochemical alterations in organs. In the following subsections, these effects will each be described, related studies reviewed, and evidence for the effect assessed in the context of its seriousness and relationship to human effects.

a) Hematological (Blood Chemistry) Effects. Hematological changes are continuously occurring in all living mammals, including humans. These alterations in blood enzyme or electrolyte concentrations are necessary to maintain homeostasis, the steady-state biological condition of normal, higher organisms. Hematological perturbations which can be induced by NO_2 exposure may be indicative of a biologically significant interference with normal function.

A continuous exposure of 0.05 ppm NO_2 for 90 days showed no alterations in the hemoglobin or erythrocyte levels of rats.[128] Depression in the glutathione (GSH) peroxidase levels of red blood cells was induced by a 7-day exposure of guinea pigs to 0.5 ppm NO_2 but disappeared after 4 months.[25,26] This suggests a possible compensatory mechanism for dealing with NO_2-induced oxidation. Continuous exposures of guinea pigs to 0.40 ppm NO_2 for one week resulted in significantly increased red blood cell D-2,3-diphosphoglycerate levels, an alteration which may be an indicator of tissue deoxygenation.[28]

The effects on hematological parameters from exposure to NO_2 described above probably occur in humans as well. Decreases in hemoglobin, hematocrit, and erythrocyte acetylcholinesterase have been found in humans exposed to

1.0-2.0 ppm NO_2 for as little as 2 1/2 hours.[39] However, it is very difficult to interpret the biological significance of these hematological perturbations. Many of the changes may simply be a normal protective response to an invading toxic agent. Comparable studies of human subjects will be necessary before the full significance of hematological effects is understood.

b) Central Nervous System and Behavioral Effects. The central nervous system controls the senses, behavior and normal functioning of the organs. A major alteration in central nervous system function could have serious biological import. However, the data base on central nervous system effects from NO_2 exposure of animals is quite limited, and the extrapolation of these effects to humans is uncertain at best.

The only central nervous system study which reported potentially serious effects showed that brain enzyme levels of guinea pigs were altered by exposure to 0.53 ppm NO_2 for 8 hours/day over 180 days.[129] Although the alterations of brain enzyme levels by NO_2 could have biological importance in human extrapolation, the study has not been replicated. While other studies have shown central nervous system effects, the effects reported are not of a sufficiently serious nature to warrant concern.

c) Biochemical Indicators of Extrapulmonary Effects. Biochemical indicators of extrapulmonary effects can be enzymes, lipids, lipoproteins, hormones, steroids, immunoglobulins, or electrolytes. These substances, which are found in the blood and various organs of the body, may provide an early warning of potentially more serious long-term effects from NO_2 inhalation. Numerous studies suggest that NO_2 causes effects including kidney, heart, and liver damage.

Enzyme markers have been identified in several different animal species including guinea pigs, rats, and hamsters. Levels of some marker enzymes have been shown to change after exposure to NO_2 concentrations as low as 0.5 ppm. A seven-day exposure of guinea pigs to 0.5 ppm NO_2 produced significantly higher lysozyme and plasma cholinesterase levels, but long-term exposure caused a decrease in both.[25,26] Release of lysozyme into the blood can be an indicator of hepatic and myocardial damage. Levels of cholinesterase tend to be elevated during cardiac surgery or hemachromatosis (blood disease) but depressed for hepatocellular (liver) disease and myocardial infarction (heart attack)[50,51] Alterations in the other enzymes (SGOT, SGPT, and LDH) measured in the Donovan et al. (1976)[25] and Menzel et al. (1977)[26] studies were suggested as being related to NO_2-induced hepatic (liver) damage or perhaps even hepatic lesions for the 4 month exposure to 0.5 ppm NO_2.

Further support for NO_2-induced hepatic damage has come from a study in which guinea pigs were exposed to 1.1 ppm NO_2 for 8 hours/day over a 180 day period; decreased plasma cholinesterase, albumin, seromucoid, alanine and aspartate transaminase were found in exposed animals[27]. Additional evidence was provided by electron micrographs of the liver which suggested intracellular edema.

A significant increase in pentobarbital-induced sleeping time was caused by 3 hour exposures to NO_2 concentrations as low as 0.25 ppm[18] In this study, mice exposed to 0.125 ppm NO_2 showed no differences from control, while female mice exposed to 0.25 ppm NO_2 and higher for 3 hours/day showed a significant increase in pentobarbital-induced sleep time. The effect disappeared at all levels after repeated exposure. It was suggested that NO_2 may alter metabolism of foreign substances (e.g. drugs, chemicals) by the liver, thus increasing the time necessary to detoxify pentobarbital and potentially other related drugs or chemicals. A related study of the effects of ozone on pentobarbital-induced sleep time revealed that less exposure time was required for NO_2 than for ozone to produce a significant effect (i.e. a single exposure of NO_2 caused more effect than a single exposure of ozone)[130].

Consistently higher levels of urinary protein were found in guinea pigs continuously exposed for 7 to 14 days to 0.5 ppm NO_2; proteinuria was also detected in guinea pigs exposed for only 4 hours/day to 0.4 ppm NO_2[76]. Analysis of the proteins revealed that they were albumin and were α, β, and σ globulins, whose presence in the urine suggests nephrotic syndrome (kidney disease). Histopathological (tissue) investigations of the kidney were reported to be negative.

d) Teratogenesis, Mutagenesis and Carcinogenesis. Teratogenic effects are those biological alterations which have some impact on development of unborn animals (e.g., fertility, litter size, birth weight, birth defects). Mutagenic effects are alterations of the chromosomal structure of normal cells, which may result in mutant cells and can be inherited.

There is little or no evidence in the literature demonstrating that exposure to NO_2 is teratogenic, mutagenic or oncogenic in animals. However, a recent report by Iqbal et al. (1980)[20] suggests concentration related *in vivo* biosynthesis of N-nitrosomorpholine in mice exposed to 0.2 ppm and higher levels of NO_2 along with morpholine for 4 hours. This is the first and only report of a direct link between NO_2 exposure and nitrosamine formation *in vivo*. While the nitrosamine quantities formed at the 0.2 ppm NO_2 exposure were too small for accurate analysis, a maximum of 2230 ng N-nitrosomorpholine/mouse was detected after 4 hours of exposure to 50 ppm NO_2 along with morpholine. Because the low level exposure to NO_2 has been related to possible concomitant biosynthesis of nitrosamines this area of investigation requires further work to assess better the potential health hazards.

A.3. Extrapolation Modeling

Animal studies permit a complete evaluation of disease in that the researcher has the choice of a wide range of concentrations, exposure regimens, chemical agents, biological parameters, and animal species. Many physiological mechanisms are common to animals and man so it can be hypothesized that, if a pollutant causes a particular health effect in several animal species, it will be likely to cause similar effects in exposed humans. However, this flexibility in animal studies is not gained without expense. Quantitatively relating effective pollutant concentrations in animals to concentration responses in man is not currently possible.

The current annual standard for NO_2 was based primarily on epidemiological data using an NO_2 chemical-monitoring method which is now known to be invalid. The only quantitative chronic NO_2 exposure studies available used animals. While the animal studies cannot provide direct evidence of effect levels in man, they do suggest that long-term exposure to

NO_2 causes emphysema in animals. If man is to be protected from such a severe irreversible effect, additional efforts must be undertaken to develop extrapolation models useful in the setting of NAAQS. Similar examples can be described for other NAAQS in which the large animal toxicological data base provides evidence for potentially severe adverse effects in man. But without extrapolation models, this information can only be used qualitatively in considering which standards provide an adequate margin of safety.

APPENDIX B. Ambient NO_2 Concentrations in Urbanized Areas

This appendix contains a summary of monitored NO_2 air quality in 186 urbanized areas of the country. The data discussed is used to develop section IV and portion of section VI.

Annual Averages

Annual average concentrations of NO_2 are available for 186 of the nation's 275 urbanized areas. The mean of the annual averages for these areas is 0.029 ppm, as compared to a corresponding value of 0.001 for isolated areas essentially unaffected by man-made NO_x emissions. The comparable figure for inhabited non-metropolitan areas is approximately 0.01 ppm. Thus, long-term NO_2 concentrations are much higher in the nation's cities than in rural areas and small cities. In addition, data in the Criteria Document[1] indicate that NO_2 annual averages in most urbanized areas are increasing.

Table 1 indicates that 95% of all urbanized areas reporting data in 1977 through 1979 meet the current annual average NAAQS of 0.053 ppm (100 $\mu g/m^3$). The highest annual average of 0.081 ppm is found in the Los Angeles area.

Daily Averages

A second method of characterizing ambient concentrations of NO_2 is through the statistical distribution of daily or 24-hour average values. Table 1 also contains this distribution in terms of the 24-hour average values which would be expected to be exceeded more than once per year. (The once per year exceedance rate was selected for this distribution because it has historically been used in setting ambient air quality standards.) For example, based on 1977-79 ambient monitoring data, no 24-hour average concentration would be expected to exceed 0.17 ppm more than once per year in 95% of the 186 areas examined. Moreover, it would not be expected that a 24-hour value of 0.24 ppm would be exceeded more than once per year in any of the areas examined.

Short-Term Averages

Similar calculations are also displayed in Table 1 for 3-hour average values. However, because continuous monitoring is not available in all 186 urbanized areas, 3-hour average data are shown for only 104 areas. As can be seen, in 95% of the 104 areas, the 3-hour average concentration levels would not be expected to exceed 0.29 ppm more than once per year. Likewise,

TABLE 1

CHARACTERIZATION OF NO_2 LEVELS (IN PPM) IN URBANIZED AREAS FOR DIFFERENT AVERAGING TIMES AND FORMS

		24-Hour Average	3-Hour Average	1-Hour Average Daily Maximum		
Distribution of Urbanized Areas	Annual Average	1 Exceedance[a]	Daily Maximum with 1 Exceedance[a]	Met 95% of days per year	Met 99% of days per year	1 Expected Exceedance[a]
Minimum	0.005	0.006	0.03	0.01	0.01	.06
50 Percentile	0.028[c]	0.075	0.14	0.06	0.09	.15
95 Percentile	0.053	0.168	0.29	0.20	0.33	.34
99 Percentile	0.063	0.210	0.31	0.32	0.35	.41
Maximum	0.081	0.242	0.40	0.38	0.48	.49
Number of urbanized areas analyzed[b]	186	186	104	104	104	104

Source of Data: 1977-1979 SAROAD data base.

Notes:
a. Expected exceedance form, when the rate is $\leq$ 1 per year.
b. The total number of urbanized areas in the U.S. is 275.
c. The mean annual average for isolated areas unaffected by man-made NO_2 is approximately .001 ppm.

the highest 3-hour average which would not be expected to be exceeded more than once per year in any of the areas examined is 0.40 ppm.

Table 1 also contains several characteristic methods of displaying the 1-hour average NO_2 concentration levels observed during 1977-79 in the above 104 urbanized areas. The first of these consists of determining the distribution of maximum 1-hour average concentrations which would not be expected to be exceeded more than once per year. This distribution corresponds with similar distributions for 24-hour and 3-hour average values previously discussed.

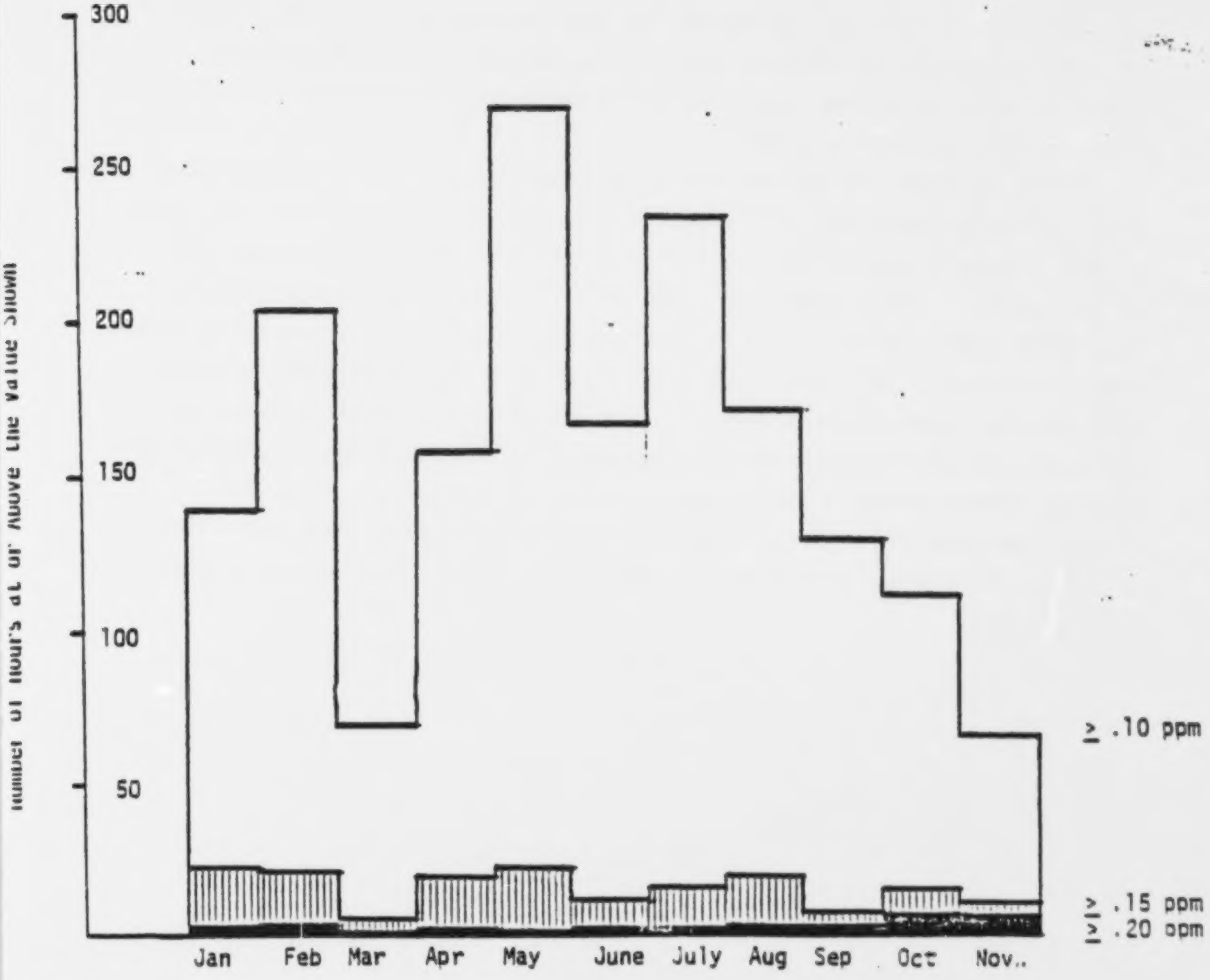
The second and third approach consist of determining the distribuiton of maximum 1-hour average concentrations (during any given day) which would not be exceeded on 95% and 99% of the days in a calendar year. These latter two approaches afford a means of measuring exposure to short-term repeated peaks of NO_2.

As can be seen from Table 1, in 50% of the areas (52 of 104) the daily maximum 1-hour concentration of NO_2 would not be greater than 0.06 ppm on 95% of the days in a calendar year (e.g., on only 18 days would the daily maximum 1-hour concentration exceed 0.06 ppm in these 52 areas). Similarly, in these same areas, the daily maximum 1-hour concentration of NO_2 would not be greater than 0.09 ppm on 99% of the days in a calendar year. As a further example, the data in Table 1 illustrate that in 95% of the areas (99 of 104) the daily maximum 1-hour concentrations would not exceed 0.20 ppm on 95% of the days or 0.33 ppm on 99% of the days.

The monthly distributon of 1-hour averages greater than 0.10 ppm, 0.15 ppm, and 0.20 ppm in 15 U.S. cities is shown in Figure 1. While in most areas the highest 1-hour NO_2 values occur in the summer months, they frequently occur during the winter in California. This tends to flatten the distribution somewhat, particularly for the greater than 0.15 ppm and greater than 0.20 ppm cases.

The distribution in Figure 1 indicates that throughout the year there are many hours when hourly levels of NO_2 exceed 0.10 ppm in these cities. However, there are relatively few hours when 1-hour levels exceed 0.20 ppm. The number of hours at or over 0.10 ppm is highest in February, May and July. The number of hours at or over 0.15 ppm, while generally represented by a flat distribution, drops off noticeably in March and September. The

Figure 1
ANALYSIS OF MONTHLY DISTRIBUTION OF
HIGH 1-HOUR NO_2 VALUES
15 cities ~ 1977 data



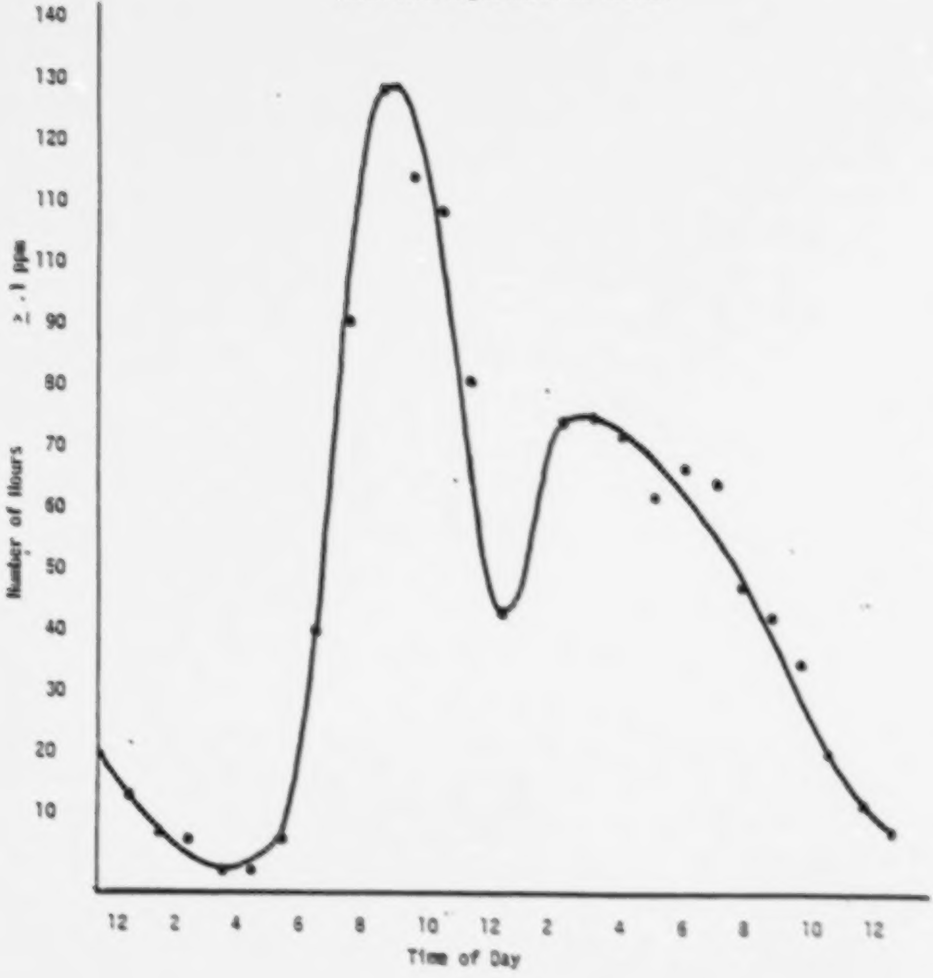
number of hours at or over 0.20 ppm is greatest in October and November; most of the cities reporting these high values are in California. While the data on Figure 1 are from 1977, a cursory review of more recent data indicates that the high 1-hour NO_2 pattern depicted in Figure 1 still holds.

High hourly NO_2 values in urban areas form a bimodal distribution throughout the day when aggregated, as shown in Figure 2. The highest peak occurs in late morning, roughly corresponding to the early-morning release from motor vehicular traffic and subsequent conversion of NO to NO_2. The second peak starts in the late afternoon and declines slowly. This peak is due to ozone titration, when ozone formed early in the day mixes with fresh NO_x emissions to form NO_2 and oxygen (by the reaction $NO + O_3 \rightarrow NO_2 + O_2$). The bimodal pattern is found in most U.S. urbanized areas although some report frequent nighttime peaks due to a slow titration reaction with ozone transported into an area.

While NO_2 peaks in the general urban scene are closely correlated with motor vehicular emissions of nitrogen oxides (and carbon monoxide), NO_2 peaks in many places do not follow the fairly repetitive pattern associated with mobile sources. These areas are often affected by nitrogen oxide emissions from large point sources, such as power plants, steel plants, and gas pipeline pumping stations. NO_2 peaks from these sources at any particular location vary greatly depending upon meteorological conditions. Areas affected by point sources are characterized by generally low levels of NO_2 punctuated by high NO_2 spikes during a fumigation or inversion situation. When this occurs, the high NO_2 concentrations are usually correlated with high levels of sulfur dioxide and particulate matter, both indicative of a common point-source origin.

Figure 2

IDEALIZED CURVE OF HIGH (> .10) HOURLY
NO_2 VALUES BY TIME-OF-DAY
(8 cities data)
(data from eight selected cities)



APPENDIX C. CASAC CLOSURE MEMORANDUM

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

July 6, 1982

OFFICE OF
THE ADMINISTRATOR

SUBJECT: CASAC Review and Closure of the OAQPS Staff Paper for Nitrogen Oxides

FROM: Sheldon K. Friedlander, Chairman
Clean Air Scientific Advisory Committee

Sheldon K Friedlander

TO: Anne M. Gorsuch
Administrator

The Clean Air Scientific Advisory Committee has completed its third and final review of OAQPS's revised staff paper entitled Preliminary Assessment of Health and Welfare Effects Associated with Nitrogen Oxides for Standard-Setting Purposes. The Committee has prepared this closure memorandum to inform you of its major conclusions and recommendations concerning the various scientific and technical issues associated with the revision of the National Ambient Air Quality Standards (NAAQS) for nitrogen dioxide, and to advise you of the scientific quality of the staff paper. This memorandum is the outcome of three CASAC review meetings of the staff paper held on November 14, 1980, February 6, 1981, and November 18, 1981. It supplements CASAC's closure letter on the air quality criteria document for nitrogen oxides sent to you on June 19, 1981. In that letter the Committee advised that the criteria document was scientifically adequate for use in standard setting.

CASAC is satisfied that its recommendations for improving the scientific quality of the staff paper have been incorporated in successive revisions of the document. It is now a balanced and thorough interpretation of the scientific evidence pertaining to this pollutant. It is also consistent with the evidence presented and interpreted in the nitrogen oxides criteria document. Thus, the Committee believes that the revised staff paper for nitrogen oxides provides you with the kind and amount of technical guidance needed to make any appropriate revisions to the primary and secondary standards.

Attachment

CASAC Conclusions and Recommendations on Major Scientific Issues and Studies Associated with the Development of Revised NAAQS for Nitrogen Oxides

A. Critical Elements in the Primary Standard Review

During the review of both the NO_x criteria document and staff paper it became apparent that no single study could provide the scientific basis for revising the primary standard for nitrogen dioxide. Rather an accumulation of evidence from animal toxicology, human clinical, and epidemiological studies furnishes both qualitative and quantitative support for a revised standard. Each class of study is subject to certain methodological limitations but, taken together, these studies provide sufficient evidence to guide you in making an appropriate public health policy decision. In addition, the Committee concludes that all of the key studies related to human health effects were identified and discussed in the staff paper. Based on a discussion of these issues CASAC recommends that you retain the annual primary standard and select the concentration level at the lower end of a range between .05-.08 parts per million (ppm). Discussed below are CASAC's conclusions and recommendations concerning the critical issues associated with revising the primary NO_2 standard.

1. Animal Toxicology Studies

Three alternatives regarding the use of animal toxicology data for standard-setting were reviewed by the Committee. These included: 1) using animal data as qualitative support in developing a margin of safety; 2) using data from animal studies as quantitative support in developing a margin of safety; 3) identifying each type of biological effect which has been found to occur in animals from exposure to NO_2 and assessing the extent to which specific studies reporting a given effect can be used to estimate the lowest effects level for humans. CASAC concludes that option 3 is the most reasonable approach to employ in evaluating a data base whose quality and relevance of animal response vary widely. Thus, the Committee recommends that results from animal studies should be considered on a case-by-case basis in making extrapolations to human health effects.

2. Human Clinical Studies

The Committee concludes that none of the controlled human exposure studies offer definitive evidence that adverse health effects occur at levels below one part per million (ppm). Studies have reported mild symptomatic effects (e.g. dizziness, headache, nasal discharge) in some sensitive population subjects after a two-hour exposure to .5 ppm (Kerr, et al, 1979). However, the Committee would not go so far as to describe such symptoms as "adverse health effects." In addition, CASAC recommends that reported results of the Orehek et al. (1976) and Von Nieding (1977) studies (i.e. dose-response curves for changes in specific airway resistance after exposure to 0.1 ppm NO_2 and a bronchoconstrictor) not be considered in establishing a lowest observed effect level. This recommendation reflects the Committee's concern over uncertainties in the statistical analysis and uncertainty regarding the significance of responses observed in studies that use a bronchoconstrictor. These studies should instead be used along with other qualitative and quantitative evidence in selecting a margin of safety for a revised standard.

3. Epidemiological Studies

Community epidemiological studies identified and discussed in the staff paper and criteria document do not provide quantitative evidence of identifiable public health effects linked to specific ambient air concentrations of NO_2. With respect to specific studies the Committee concludes that the Chattanooga (Shy et al., 1970, 1973 and 1979) and the Japanese (Kagawa and Toyama, 1975) studies do not establish quantitative dose-response information for revising the present standard. The studies do provide, however, limited qualitative support for the hypothesis that higher levels of NO_2, in association with other pollutants in the ambient air, may affect lung function and/or the onset of respiratory illness in children.

The Committee devoted considerable discussion to epidemiological studies assessing NO_2 exposures to people residing in homes with gas stoves. These studies have reported a higher incidence of acute respiratory disease for children living in homes equipped with such stoves than for those residing in homes in which electric stoves were utilized. Although gas stoves tend to emit large amounts of NO_2, numerous other factors (e.g. humidity, carbon monoxide, formaldehyde) may affect and confound the results of the studies. The

Melia et al. (1977, 1979) studies do not provide quantitative dose-response data for NO_2 exposures due to the absence of short-term NO_2 measurements in the residences of the subjects evaluated and due to incomplete analysis of the aforementioned possible confounding or covarying factors. In a limited qualitative sense, however, the studies do suggest an association between higher NO_2 levels and increased respiratory symptoms and illness in children.

CASAC also evaluated the Harvard "Six Cities Study" during its (Speizer et. al. 1980) review of the staff paper and criteria document. This study was designed to gather information on long-term health effects. The increased incidence of respiratory disease reported in the "Six Cities Study" may be caused by repeated short-term peak exposures rather than long-term NO_2 concentrations of 24 hour or annual averages; however, this has not yet been conclusively demonstrated due to the scarcity of short-term indoor NO_2 monitoring data. In using the Six Cities Study data, both the study authors and CASAC caution the Agency against data overinterpretation of this study in selecting revised NO_2 standards.

4. Short-Term vs. Long-Term NO_2 Standard, and Scientifically Acceptable Ranges for a Revised Standard

The Committee spent considerable time discussing the extent to which available animal, human clinical, and epidemiological studies cited in the staff paper provide a scientific basis for retention of an annual primary standard. It also reviewed whether such evidence would provide scientific support for the establishment of a short-term (1-3 hour) primary standard. Evidence reviewed by the Committee clearly documents the existence of health effects due to short-term peak exposures that are distinct from the effects associated with longer-term average exposures. The evidence does not, however, distinguish whether the latter effects are the result of a series of short-term peak exposures or the result of lower level long-term exposures or some combination of both. The CASAC has concluded that any revised NO_2 standard needs to offer sufficient protection against both the short-term as well as the long-term reported effects.

For both scientific and practical reasons related to the implementation of standards, the Committee recommends that you retain an annual standard and that you do not need to establish a separate short-term primary standard at this time. Qualitative support for an annual standard is based on results from animal test data. For example, from animal inhalation studies in which several species were used, investigators have reported that long-term NO_2 exposures produced structural alterations in the distal bronchioles and alveolar regions of the lung at long-term NO_2 levels in the range of .25 - .50 ppm. Quantitative evidence of short-term effects at higher NO_2 exposure levels (.5 ppm NO_2) has been reported in human clinical studies. Community epidemiological and "gas stove" study data furnish additional support for retaining the annual primary standard. In particular, the "gas stove" studies suggest that multiple exposures to short-term NO_2 levels below 0.5 ppm are of concern and should be avoided in the ambient air. For example, the "gas stove" studies and related studies in which NO_2 was measured in homes utilizing gas stoves suggest that repeated short-term peaks in the range of 0.15 - 0.30 ppm may be of concern for children and thus should be limited in the ambient air. Revision of the primary annual standard to control long-term NO_2 concentrations can however, be set at a level that also provides adequate protection against repeated short-term peak exposures.

The staff paper suggests an annual standard set within the range of .05-.08 ppm. Based on the above discussion, the need to provide adequate protection against repeated short-term peak exposures, and due to the uncertainties of the data base, the CASAC recommends that you consider selecting a primary annual standard level at the lower end of the .05-.08 ppm range to ensure an adequate margin of safety of protection against both long-term and short-term health effects. The factors you should consider to determine a margin of safety and to identify the sensitive population groups are appropriately discussed in the staff paper.

Factors related to the implementation of the standard were also discussed by CASAC. Retention of an annual average standard would be the least burdensome option for the states to incorporate into revised State Implementation Plans (SIPs) because individual SIPs already are based on such an approach.

B. Critical Elements in the Secondary Standard Review

The Committee is satisfied with the scientific quality of the staff paper's presentation of information concerning welfare effects. The discussion of materials damage, personal comfort and well-being, vegetation effects, and visibility impairment was comprehensive and well written.

Acidic deposition is also a welfare effect associated with the oxides of nitrogen. Because of the great complexity of this issue CASAC had previously recommended that the Agency prepare a Critical Assessment Document for Acidic Deposition that would evaluate the contribution of NO_x and other precursor pollutants to the formation, transport, and effects of the total acidic deposition problem. CASAC thus agrees with the OAQPS staff decision not to address acidic deposition in the NO_2 staff paper, and it looks forward to the submission of the critical assessment document for its review.

CASAC concurs with the staff paper recommendation that an annual primary standard within the range of .05-.08 ppm will offer sufficient protection for the various welfare effects of concern.

Summary

CASAC recognizes that your statutory responsibility to set standards requires both scientific and policy judgments to protect public health and welfare. While the Committee is willing to further advise you on the NO_2 standards, we see no need, in view of the already extensive comments provided, to review the proposed NO_2 standards prior to their publication in the Federal Register. In this instance the public comment period will provide sufficient opportunity for the Committee to submit any additional comment or review that may be necessary.

The Committee made scientific and editorial comments during the review of the revised staff paper. These remarks, as well as a more detailed discussion of the conclusions and recommendations provided above, are included in the transcripts of the three CASAC meetings (held on November 14, 1980, February 6, 1981, and November 18, 1981) to review this document. With the understanding that these minor changes will be incorporated in the final staff paper, the Committee is satisfied that this document is scientifically adequate for use in standard setting.

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